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ANIMAL DRUG AMENDMENTS AND PATENT TERM RESTORATION ACT OF 1986

HEARING

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

NINETY-NINTH CONGRESS

SECOND SESSION

ON

S. 2407

ENTITLED THE "ANIMAL DRUG AMENDMENTS AND PATENT TERM RESTORATION ACT OF 1986"

JULY 18, 1986

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ANIMAL DRUG AMENDMENTS AND PATENT TERM RESTORATION ACT OF 1986

FRIDAY, JULY 18, 1986

U.S. SENATE,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
Washington, DC.

The committee convened, pursuant to notice, at 10:05 a.m., in room SD-430, Dirksen Senate Office Building, Senator Orrin G. Hatch (chairman) presiding.

Present: Senators Hatch, Metzenbaum, and Simon.

OPENING STATEMENT OF SENATOR HATCH

The CHAIRMAN. Many of those attending this hearing today may experience a sense of deja vu. Just 2 years ago, this committee considered and Congress ultimately passed the Drug Price Competition and Patent Term Restoration Act, legislation I introduced along with our colleague in the House, Representative Henry Waxman. Our legislation had two simple goals. First, to encourage competition in the pharmaceutical industry by dramatically expanding the Food and Drug Administration's ability to approve generic drugs. And second, to provide an incentive for the research-based pharmaceutical companies to continue their trail-blazing efforts at research and development by restoring marketing time lost during the expensive and time-consuming FDA approval process.

Now, those goals have been met—and exceeded. Nine of the top selling brand name drugs now have approved generic equivalents—at significantly lower prices. The Commerce Department reported recently that generic drugs are selling so well that consumers may exceed the $1 billion in savings over 10 years that the President predicted when he signed this legislation.

The act has also heightened investment and has provided patent term protection for several pioneer products. So this is one case where everyone benefits, as planned—consumers, the pharmaceutical companies, even the Government, which buys more than 2.5 billion dollars' worth of drugs each year.

Well, that kind of performance really provides a hard act to follow. But the committee staff and I figured, as they used to say, we did it before, so we think we can do it again.

Although we are talking about a smaller market, why not extend the same kind of benefits to pharmaceutical companies producing drugs for veterinary purposes?

Why not reduce the costs of hard-pressed livestock and dairy producers and help provide less expensive food products for consumers?

Why not extend the benefits of lower veterinary costs even to pet owners?

So we introduced S. 2407, the Animal Drug Amendments and Patent Term Restoration Act of 1986, which would indeed apply the same reforms of the Drug Price Competition and Patent Term Restoration Act to veterinary medical products.

The act would allow the submission of abbreviated new animal drug applications for generic equivalents, avoiding expensive and time-consuming duplicative testing for the previously approved brand name drug, with a showing that the drug is bioequivalent to the previously approved drug.

The act would also restore up to 5 years of the patent term for pioneer animal drugs to make up for exclusive marketing time lost in the FDA approval process.

I am looking forward to the testimony of our witnesses today from the FDA, the pharmaceutical industry, and the veterinary medical community. Although we may find a few kinks to be worked out, I am sure you will agree with me that this legislation too will benefit all parties involved through greater competition, lower costs and improved incentives for new research and investment.

At this point, we will keep the record open for statements by other Senators.

We are pleased with the witnesses we have today. Our first panel is from the Food and Drug Administration. I must say that it is always a real pleasure for me to welcome our own Commissioner Frank Young, who today is accompanied by John Norris, Deputy Commissioner; Mr. G. Guest, the Acting Director for the Center for Veterinary Medicine, and Tom Scarlett, the Chief Counsel.

Mr. Young, I want to tell you how much I admire you and how much I appreciate your leadership in these areas. I also want to thank you for the help that you and everybody else involved in this process have personally given to me. You have won tremendous respect and appreciation in this town and across the country for the work you have done, and the fairness that you have exhibited, handling this position. It is a tough position, and there is a lot of criticism for it. I think FDA is the best agency in Government today. There are others that come close, of course, but I am particularly proud to work with this agency, and I have been very proud to work with you and your colleagues here with you today.

So we will turn the time over to you.

STATEMENT OF DR. FRANK E. YOUNG, COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY JOHN NORRIS, DEPUTY COMMISSIONER; G. GUEST, ACTING DIRECTOR, CENTER FOR VETERINARY MEDICINE, AND THOMAS SCARLETT, GENERAL COUNSEL, WASHINGTON, DC

Dr. YOUNG. Thank you very much, Mr. Chairman, for those very kind words. It truly has been a pleasure and a privilege for me to serve the agency now a little over 2 years, and I know I can speak for my colleagues in our commitment to our high calling for public service and the high regard we hold the office and the opportunity to serve.

We would like to compliment you for your leadership in this field because we think that this bill is a very important extension of what you have previously done in collaboration with Mr. Waxman to ensure that drugs can be brought to the American people in a safe form and in a form that will be economical.

It is interesting to note that through that act, we have formed an office to deal with the generic drugs, and we will do the same as we strongly support this bill. If it goes to law, we will provide a division for meeting with the approval of generic drugs. We think it is important for the very reasons that you emphasize.

First, it will extend the patent life, thereby encouraging innovation. Through our action plan, we hope to reduce and shall reduce the approval time, thereby making the patent extension even more meaningful. The consumer benefits through lower prices, by obtaining high-quality drugs for their animals, both domestic pets as well as our food animals, in a much more effective way.

We feel that the adverse reporting of generics as well as pioneer human and animal drugs will add an additional layer of safety so that we can continue to monitor this process.

We are also confident that the emphasis on bioequivalency that is placed in your bill will meet the major requirements for safety. And I would like to introduce for the record a recent graph that FDA will soon be publishing, which demonstrates that if one looks at 184 different drugs on post-1962 ANDA human drugs, one sees a very sharp, bell-shaped curve on the bioequivalency of generics as compared to the pioneer drug with a standard deviation of 3.5 percent. The bioequivalency is a very good indicator and has been very close in these generic drugs.

We pledge to you, as we did with the human drugs, that if we have the appropriate mechanisms and resources in place that we will meet, as we have, and exceed, as we have, the approval time. And as you know, in our action plan we are now approving 95 percent of the generic drugs below the 180-day time; in fact, 95 percent in 140 days.

So the Food and Drug Administration is pleased to support your bill. We will be delighted to work in any ways that we can on any technical concerns that you have.

And at this point, Mr. Chairman, we are prepared to answer your questions.

[The prepared statement of Dr. Young and the graph referred to follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT

BY

FRANK E. YOUNG, M.D., PH.D.

COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

JULY 18, 1986

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman:

I am pleased to have this opportunity to discuss our views on S. 2407, the "Animal Drug Amendments and Patent Term Restoration Act of 1986."

This legislation would revise the requirements for the premarket approval of new veterinary drugs by authorizing an abbreviated application procedure for generic, or duplicate versions of "pioneer" drugs. It also would authorize the restoration of patent time lost due to the premarket requirements of both the Federal Food, Drug, and Cosmetic (FDC) Act for veterinary drugs and the Virus-Serum-Toxin Act, administered by the Department of Agriculture, for veterinary biologicals. S. 2407 thus would extend to veterinary products those benefits already established for human drugs through the milestone legislation that you sponsored in 1984.

Mr. Chairman, we strongly support the dual objectives of S. 2407. The concept of an abbreviated approval process coupled with patent term restoration has received high priority by this Administration, and is embodied in Title V of the Administration's proposal, the "Intellectual Property Rights Improvement Act of 1986," introduced as S. 2525 on June 6, 1986. As my predecessor testified before your Committee in 1984, we firmly believe that this balanced concept represents a public health objective whose time has come. Let me briefly explain why.

The Benefits of Abbreviated Applications

An abbreviated new animal drug application is a vehicle for obtaining marketing approval from the Food and Drug Administration (FDA) for a

duplicate version of a drug product that has already been approved as safe and effective. An abbreviated application does not contain the data on safety and efficacy that were required in the full new animal drug application to market the original, or "pioneer" drug. It is predicated on the view that the safety and effectiveness of the drug have already been established.

Requiring a repetition of the costly and time-consuming studies that are typically required to establish safety and effectiveness has the effect of barring the development of most generic equivalents. Without an abbreviated procedure, the requirement for a full marketing application usually results in a formidable barrier to market entry--in effect, a secondary patent--that protects the pioneer indefinitely from generic competition. Moreover, a requirement for duplicative studies is scientifically unnecessary and ethically questionable because it causes needless use and sacriface of experimental animals.

FDA has long recognized the value of an abbreviated application system for both human and veterinary drugs. Abbreviated applications have been permitted by FDA for years for the approval of generic versions of both human and veterinary drugs first approved only for safety between 1938 and 1962, the year in which Congress amended the FDC Act to require that drugs be shown to be effective as well as safe. As a consequence, approximately half of the $1 billion veterinary drug market is currently eligible for abbreviated applications. As you know, however, the abbreviated application procedure that was

established by statute in 1984 for post-1962 human drugs, did not include post-1962 veterinary drugs. We agree with you that there is no valid reason for this distinction between human and veterinary drugs--and also between pre-1962 and post-1962 veterinary drugs--to continue.

The Benefits of Patent Term Restoration

We strongly believe, moreover, that legislation to establish abbreviated applications must also provide patent term restoration for pioneer drugs in order to encourage innovation of new products. The law enacted in 1984 contained both features for human drugs and S. 2407 wisely follows suit. Sound public policy demands linkage of the two concepts in order to encourage competition and lower prices through the development of generic drugs and at the same time foster research for new products through patent term restoration.

The Department of Health and Human Services traditionally has supported the extension of patents associated with products that require the premarket approval of FDA. These products often entail high development costs, the risk of failure and small potential markets. This is particularly true for many veterinary drugs. They are often developed for narrow, specialized markets and are more susceptible to economic influences, such as those that affect agribusiness, than their human counterparts. In addition, veterinary drug innovators like human drug sponsors typically lose years of patent protection because of testing requirements and regulatory review. We

are mindful of the paradox that the careful and time-consuming scientific review needed to confirm safety and effectiveness may have the effect of reducing incentives to develop new veterinary drugs. Streamlining the regulatory process will help. Nonetheless, the FDA premarket approval system must continue to be thorough enough to assure safety and effectiveness, even if that means living with a process that takes time. We want to encourage innovation, but not at the expense of safety or effectiveness. Consequently, we support patent extension for veterinary drugs as a means of encouraging innovative research.

FDA's Experience

FDA has the expertise to implement both patent term restoration for innovative veterinary drugs and abbreviated applications for generic veterinary drugs. Much of this expertise has, of course, been obtained as a consequence of the Drug Price Competition and Patent Term Restoration Act. Within weeks of its enactment in September 1984, Congress appropriated $3,200,000 for implementation, thus providing FDA with funds for 73 additional positions.

Our Office of Health Affairs assumed responsibility for implementing the patent restoration provisions of the 1984 law that involve FDA. That office has developed proposed regulations that were published last week relating to FDA's review of applications for the extension of patents and is developing a Memorandum of Understanding with the Patent and Trademark Office to assist both agencies in their mutual administration of the law. It is evident that the owners of these

patents are using the patent extension opportunities that are now available. The Office of Health Affairs has now reviewed 58 applications for the extension of patents. Indeed, over 75 percent of innovator drugs approved by FDA in 1985 have patent extension applications pending for them.

As I indicated earlier, FDA already has considerable experience with generic products, both human and veterinary. Generic versions of veterinary drugs originally marketed before 1962 have been available to consumers for years after having been approved by our Center for Veterinary Medicine on the basis of abbreviated applications. Approximately 150 such drugs have been marketed to date with an excellent record of safety and effectiveness. On the human drug side, our Center for Drugs and Biologics have approved approximately 1,450 generic versions of pre-1962 drugs (not including approvals for different dosage forms and strengths for the same drug). We have received approximately 1,250 abbreviated applications for post-1962 generic drugs (including applications for different dosage forms and strengths) since the 1984 law became effective. Approvals of post-1962 generic human drugs are now approximately 150.

S. 2407: Generic Drug Provisions

S. 2407 follows the same general structure as the 1984 law, with some significant modifications that take into account key differences between human and veterinary drugs. The provisions of the bill involving abbreviated applications essentially track FDA's existing policies and procedures for the review of generic drugs while generally providing the Agency with the flexibility to permit our procedures and

requirements to evolve along with the state-of-the-art, as well as to make case-by-case scientific judgments regarding certain types of data needed to support abbreviated applications now. While we do feel that a number of modifications to the bill are needed, we clearly support its fundamental approach.

More specifically, the bill would require that anyone who plans to market a copy of a previously approved veterinary drug submit to FDA evidence that: (1) they can make the drug according to FDA's stringent manufacturing requirements; (2) the drug can be expected to have the same therapeutic or other desired effect (i.e., that it can deliver to the site of drug action the same amount of active ingredient as does the innovator's product); (3) the proposed product meets appropriate requirements for stability, purity, strength and quality as does the innovator's product; and (4) the drug is appropriately labeled including required warnings and other information.

I would like to point out that a generic veterinary drug approved under an abbreviated application is subject to the same adverse reaction reporting requirements as is a pioneer drug. This would hold true for abbreviated applications approved under S. 2407 as well. Our system, moreover, is capable of distinguishing between a report on a pioneer veterinary drug and on a generic. To date, we have not been able to document cases where an adverse reaction was reported soley for a generic; in all cases, similar reactions have been reported for the pioneer as well.

Human Food Safety

In addition, a critical factor in the review of veterinary drugs that is taken into account in S. 2407 is concern for human food safety. As part of the approval process, pioneer sponsors are required to establish the safe levels, if any, of residues of their drugs in the meat, milk and eggs produced by animals administered the drugs. They also have been required to establish withdrawal times--that is, the length of time prior to marketing of edible products that the drugs must be withdrawn from use in the animal so that the residue of the drug will deplete down to a safe level.

Because the pioneer has established a safe level for the drug, it will be unnecessary for the generic manufacturer to do so. Furthermore, the generic applicant can receive the same withdrawal time that is established during the approval of the pioneer drug by submitting data to satisfy FDA that the residue depletion time for the generic drug is the same as that for the pioneer.

For many generics, a comparable depletion time can be assured from a showing that the rate and extent of absorption into the blood and rate of depletion out of the blood or other bodily fluid does not show a significant difference from the of the pioneer (i.e., that the generic drug is "bioequivalent" to the pioneer drug). However, there are instances in which an analysis of blood or body fluid concentrations cannot provide adequate information about depletion of drug residues in the edible muscles or organs of the animal. Under such circumstances,

studies measuring the rate of disappearance of residues in these tissues are needed to establish the withdrawal period for the generic drug.

FDA's Center for Veterinary Medicine is experienced in making judgments about when such data must be provided. We commend S. 2407 for providing FDA with the flexibility necessary to exercise our judgment in this significant aspect of generic veterinary drug review.

Another important food safety consideration for veterinary drugs is the potential for inactive ingredients to leave residues in food-producing animals. For the majority of inactive ingredients a generic manufacturer may use in a product, a residue hazard does not exist, because most ingredients are safe. However, FDA should have flexibility to require safety information whenever the Agency does not have enough information about a particular inactive ingredient that is proposed for use in a generic product to be confident of its safety. Presently, S. 2407 would allow FDA to reject an abbreviated application only if information shows the inactive ingredient to be unsafe. We believe that more flexibility here is essential and would be pleased to work with you on this provision.

Conversely, we urge that the bill actually contain less flexibility in another area relating to food safety concerns: the establishment of tolerances, or safe levels, for animal drug residues in food. As

drafted, S. 2407 would permit applicants to submit petitions in advance of an abbreviated application for changes in existing residue tolerances. We believe that the extensive scientific data needed to support a change in a tolerance is not compatible with an abbreviated application, and would not be entertained by FDA outside of a full application. The establishment of a safe level or tolerance for an animal drug residue in food involves the review of extensive toxicologic information from short-term and long-term studies, as well as the determination of food consumption estimates in forming our position on maximum allowable levels of the drugs. Consequently, we urge that the provision permitting a petition to change a tolerance through an abbreviated application be dropped.

Other Generic Drug Provisions Significant to Veterinary Drugs

The bill addresses other areas that are significant to veterinary drugs. One area involves the many animal drugs that have been approved for use in more than one animal species. We believe that it is scientifically unnecessary to require bioequivalency and residue depletion studies in all species for all multiple species drugs. We believe that S. 2407 is correct in not requiring such studies. However, there are circumstances in which interspecies differences in the bioavailability of certain drugs make extrapolation from one species to another difficult or impossible. A generic animal drug law should, therefore, permit FDA to require studies in more than one species when it is scientifically necessary. Since S. 2407 as

currently drafted would not permit us to do this, we would welcome the opportunity to work with you to add some flexibility into the legislation on this point.

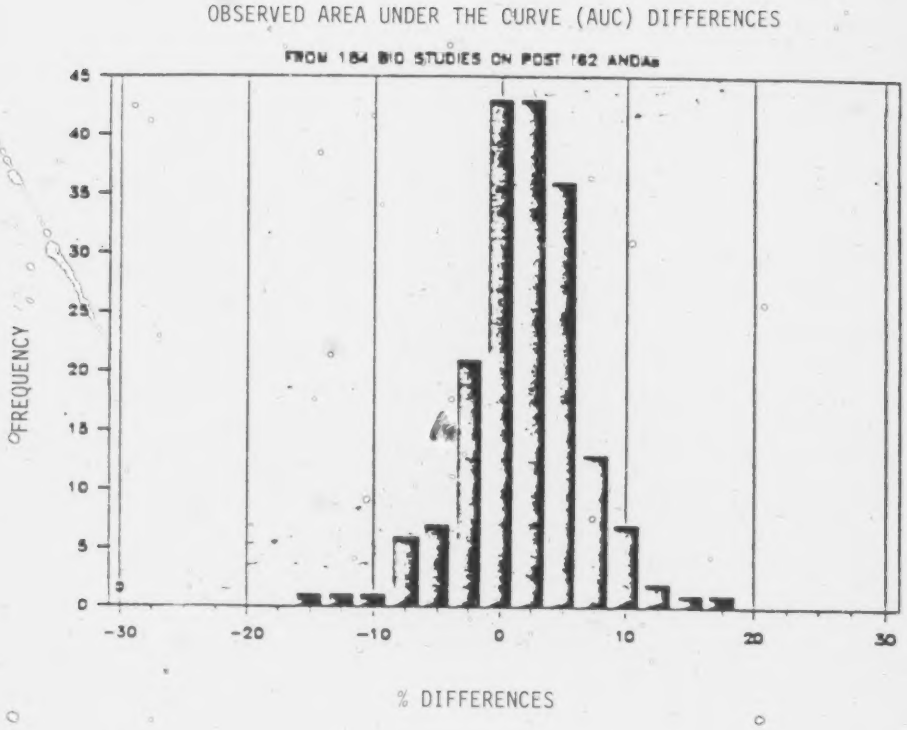
Still another important difference between human and animal drugs is the fact that a significant number of animal drug approvals are for the administration of drugs in animal feed. Such uses are primarily for improved production performance (e.g., increased rate of gain and enhanced feed use efficiency). We believe that approvals of generic versions of such drugs should be provided for in any generic animal drug law, and S. 2407 does this. Among other things, the bill specifically permits alternative means of establishing bioequivalance where measurement of blood or fluid levels of the drug is impractical. Such alternative studies are especially important for feed use drugs because fluid concentrations of the drug are ordinarily so low that a bioequivalency cannot be practically determined by ordinary methods.

Conclusion

In summary, your legislation balances the need to promote innovation through patent restoration and to foster competition through abbreviated applications for generic versions of veterinary drugs.

Mr. Chairman, the resources that we have received from implementing the patent restoration and human generic drug law of 1984 have been more than paid back to the public both in terms of the availability

of safe and effective generic products and in incentives to drug innovation. FDA has demonstrated its ability to manage the additional responsibilities that the legislation has entailed. We fully expect that we could perform the same service for the American public with veterinary drugs if your legislation is enacted. This concludes my formal statement. I will be happy to answer any questions you may have.


OBSERVED AREA UNDER THE CURVE (AUC) DIFFERENCES
FROM 164 BIO STUDIES ON POST '62 ANDAs
FREQUENCY
45
40
35
30
25
20
15
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5
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-10
0
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30
% DIFFERENCES

The CHAIRMAN. Well, thank you so much, and I appreciate your summary here this morning.

Since the early 1970's, the Food and Drug Administration has had an active generic drug policy for animal drug products originally marketed before 1962. Am I correct on that?

Dr. YOUNG. That is correct.

The CHAIRMAN. OK. Has not FDA approved many generic applications?

Dr. YOUNG. Yes, we have, but this legislation provides that we can now look at the post-1962. These drugs that were approved were pre-1962. It extends our authority and makes it more clear cut and enables us to put in place better processes.

The CHAIRMAN. You have somewhat indicated there are not very many differences from a bioequivalency standpoint. Have you noticed, though, many differences in your experience at FDA between generic drugs and pioneer drugs that are copied by generic drug companies?

Dr. YOUNG. I am sorry, Senator?

The CHAIRMAN. Have you noticed much bioequivalent differences between generic drugs and their pioneer copies?

Dr. YOUNG. No, we have not. Even as we have looked at this in the animal drug field and in the limited ones that we have approved, we do not have any reason to suspect that bioequivalency will not be a good indication, just as it has been in human drugs.

The CHAIRMAN. Dr. Young, have any significant problems arisen from the 1984 human patent term legislation which we should take into account before we finally approve this particular animal drug bill?

Dr. YOUNG. No, we do not know of any significant problems that have occurred. There have been some concerns about bioequivalency. Dr. Morrison has addressed these very forthrightly, and we will soon have published in one of the leading medical journals the graph that I showed and introduced for the record, as well as a very detailed accounting of our experience on bioequivalency.

We have been pleased with the record to date.

The CHAIRMAN. That is great. I understand that you expect a rather large influx, of abbreviated applications. Do you have adequate resources to meet this important function of resolving those problems?

Dr. YOUNG. We would recommend as an agency that it is prudent management for the Congress to do just what it did with the 1984 patent term restoration. In that case, the Congress kindly provided 73 full-time equivalents and $3.1 million, and we in turn guaranteed that we would meet the statutory limit.

I am pleased to tell you that we fully have met it. I am sorry to say that this is the only statutory limit that we have met, but this is one in which we have the full 180 days.

And one of the things I have tried to do for Congress and the administration is say that we can get the job done, but we need to have the resources, and we feel that if we were provided those appropriate resources, we would be able to fully meet the requirements.

The CHAIRMAN. Well, please work with us and make sure that we do what is necessary, because I really believe this type of legislation is crucial.

I cannot tell you how much I appreciate your coming in and supporting it, because I think that means a lot toward getting it through and getting it through a little more easily, hopefully, than we did patent term—I hope I do not have another root canal during the negotiations on this one, as I did during the 1984 human bill negotiations.

Dr. YOUNG. Well, the interesting point that you made in regard to the savings——

The CHAIRMAN. We almost lost two of the great leaders in the pharmaceutical industry. I almost killed them myself. I had that root canal, and it just got so unbearable that there was almost a murder completed—two murders—in my office that day.

Dr. YOUNG. Well, it makes it very tough when you have something like that medically going on amidst all of the crisis.

The CHAIRMAN. Well, the bad thing about it was—and I apologize to you for interjecting this—but they were probably right, and I was probably wrong; I was just in a bad mood, that's all—after 2 weeks of 18 hour days.

Dr. YOUNG. Well, parenthetically, I was told when I was dean that it is very important to have a medical affliction when you are in a very difficult discussion. The one that they recommended that was that a dean should always have hemorrhoids, and that is so that when someone comes in and petitions for funds, he can always have a pained look. I am sure your root canal was far worse.

The CHAIRMAN. Well, I think there were some people with hemorrhoids there that day, too.

Well, we appreciate your being here, and we really appreciate your support for this bill.

Let me turn to Senator Simon if he has any questions.

Senator SIMON. I do not. I am here to learn, Mr. Chairman, and I assume the Commissioner is the person who can impart great wisdom to me.

The CHAIRMAN. Thank you so much.

I do feel there are people who could impart great wisdom to you, but you have been very good at doing it for me, too, I will tell you—just wonderfully.

I appreciate having you here today, Senator Simon.

Let me just thank you again for being with us on this bill. That means a lot to those of us who are supporters of it, and I think most everybody will support it in the end, because it is right.

Senator SIMON. Forgive me, Mr. Chairman. Has the Commissioner testified already, and I was absent?

The CHAIRMAN. Yes.

Senator SIMON. OK. Then I am too late to get your wisdom, but I shall read it.

The CHAIRMAN. Well, he testified and said that he supports this bill and feels it is the right way to go.

Senator SIMON. Let me ask one question that I was just discussing with my staff just before. That is, the residue question.

In concept, I am for the bill, and when it comes to dogs and cats and pets, there is no problem. When it comes to things we con-

sume, then it seems to me there is a potential problem in the residue, that you ought to be able to prove that there is no harmful effect there.

As the bill now stands, are we being protected adequately in that area?

Dr. YOUNG. We basically feel that we are being protected adequately in this area. The important issue that we look at is the issue of bioavailability of the drug.

Since the pioneer has been on the market for a long time, and since there is a large amount of information in the literature, we know the types of inactive ingredients that would be there, the single active ingredient, and we can measure it from bioavailability. And if we plot, as we had with the human drugs and can demonstrate a very nice correlation—I am sorry you cannot see it from where you are sitting, but zero is right here, and the standard deviation between, in 184 human drugs and their generic equivalents—is about 3.5 percent. So the active ingredient in bioavailability is not deviating at all in a significant fashion from the pioneer.

If we know that, then, the only problem of residue would be in inactive ingredients, and we can look at that and determine those with just the same surety that we have to determine the inactive ingredients in the pioneer. Those are primarily done by chemical information that is submitted to us. The company must submit information on the inactive ingredients, and we feel that if we examine the combination of inactive and active, we can control the approval process appropriately.

Senator SIMON. All right. Now, you are talking to a nontechnician here, so if I ask questions that do not make too much sense——

Dr. YOUNG. I am sorry.

Senator SIMON. In the case of human beings, you do not test for residue, right?

Dr. YOUNG. That is correct. But in the animals, since we know the drug is equivalent biologically, that it is absorbed and it is distributed in the tissue in the same way as in the pioneer, and we know how the pioneer leaves residues or does not leave residues, we can make a very good prediction about how the generic drug would relate to the pioneer.

It is the advantage of knowing 20 years of experience about the pioneer and thus matching bioequivalency. Now, I know there have been some concerns on this, and we have carefully addressed them. I asked the very same question that you asked of our center people, and they have reassured me that the bioequivalency is a good measure of the residue, as long as we are able to also monitor any inactive ingredients that may be there as well.

Senator SIMON. And I guess that is the followup question. We are going to be actively monitoring this, so that we are going to take chickens and steers and others and watch very carefully what happens, so that if there is a problem, you will let us know immediately?

Dr. YOUNG. That is correct. We are going to determine problems rapidly and we are going to do it through postmarket surveillance. We will look at the drug after it is on the market in just the same

way as we do with the pioneer for the generic, and we are going to do that for the human drug as well.

We have looked at this in the past. The conventional wisdom is that there have been no problems uncovered by postmarket surveillance.

Senator SIMON. All right. Then, just kind of a final general question. From your perspective, there is no added risk that we are creating by moving ahead with this?-

Dr. YOUNG. From our perspective, there is no added risk that you are creating by moving ahead.

Senator SIMON. All right. I thank you, Commissioner.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Simon.

Thank you so much, Mr. Commissioner, and your colleagues. We appreciate all of you, and we have appreciated, too, these many years we have worked together.

Thank you.

Dr. YOUNG. Thank you very much.

The CHAIRMAN. We look forward to working together with you on this.

Dr. YOUNG. We will do anything we can to support you.

The CHAIRMAN. Thank you so much.

Our second panel is from the Animal Health Institute. Dr. James Gillin, chairman-elect, is accompanied by Eugene Lambert, general counsel of AHI, and Robert Sieck, of Eli Lilly.

Gentlemen, we are happy to have you with us, and we look forward to taking your testimony at this time.

Dr. Gillin, go ahead.

STATEMENT OF DR. JAMES GILLIN, CHAIRMAN ELECT, ANIMAL HEALTH INSTITUTE, ACCOMPANIED BY EUGENE LAMBERT, AHI GENERAL COUNSEL; AND DR. ROBERT SIECK, AGRICULTURAL ANALYTICAL CHEMICAL DIVISION, ELI LILLY & CO.

Dr. GILLIN. Thank you, Mr. Chairman.

Mr. Chairman, members of the committee, I am Dr. James Gillin, president of MSD AGVET Division of Merck & Co. and chairman elect of the Animal Health Institute.

Accompanying me is AHI's general counsel, Eugene Lambert, with the law firm of Covington & Burling, and Dr. Robert Sieck, agricultural analytical chemistry division of Eli Lilly & Co.

AHI is the national trade organization whose 52 member companies are the major manufacturers of the animal health products—that is, feed additives, veterinary drugs and biologics—marketed in the United States.

We appreciate this opportunity to testify today to discuss the issues of abbreviated new animal drug applications and patent term restoration for animal health products. We recognize that members of this committee dealt with somewhat similar issues in the human drug PTR/generic legislation that was enacted in 1984.

The main thrust of my testimony today will be to point out the fundamental differences between human use drugs and animal drugs and to show this committee why, because of those differences, animal drugs should not be treated, either in generic approv-

als or in patent term restoration, as if they were simply analagous to human use pharmaceuticals.

We request our full statement be included in the record of this hearing, and that we be permitted to augment our presentation appropriately.

In the time afforded me, I will summarize the highlights of our position, particularly how animal drugs are different from human use drugs.

Over 80 percent of animal drugs are used to treat food-producing animals. The balance are used to treat companion and exotic animals.

The sponsors of food animal drug products must demonstrate prior to marketing not just that they are safe and effective in the target species—for example, cattle, sheep, swine or poultry—but most importantly, that animal drug products will cause no health hazards to human consumers of animal-derived food.

Food animal drugs in the form they are most frequently administered—that is, in feed or water to herds of animals or flocks of poultry—vary significantly in formulation and method of administration from well-defined human drugs.

Food animal drugs are commonly used not only to treat or prevent diseases, but also to enhance weight gain and/or to improve feed efficiency—economic goals with no counterpart in the human medicine field.

While human use drugs are destined for only one homogenous species, an animal drug is often marketed for several, often disparate species as varied as chickens and cattle. The pioneer firm that develops a new animal drug must conduct a variety of tests to show that his product is safe and effective in each target species and that its use in each species will pose no human health hazards from unsafe residues.

This raises issues beyond the ability of a single species bioequivalent study to resolve.

Food animal drugs are marketed on an entirely different basis than are human health drugs. It is a fundamental fact of agricultural life that livestock and poultry producers as well as dairymen and egg producers, with their legitimate concern with profit margins, will only purchase an animal drug if its use demonstrates an economic benefit to herd and flock and production. In contrast, the decision to use a human drug is based on the health needs of a specific person.

In what ways do we believe the provisions of S. 2407 should be modified?

Bioequivalence is FDA's term for the demonstration that a generic product is biologically equivalent to the pioneer or already approved drug—that is, that the generic is safe and efficacious in the same manner as the original.

Under S. 2407, the manufacturer of a generic animal drug could satisfy FDA that it is bioequivalent to the pioneer product in cattle and, without additional data, gain approval for administration to chickens, swine, and other species without having proved that it was also bioequivalent in these species.

In short, S. 2407 presumes that a generic product will be bioequivalent in all species if it is found bioequivalent in one.

AHI urges this committee to reconsider this presumption that bioequivalence can generally be extrapolated from one species to another. The digestive system and other physiological traits of a chicken are clearly very different from those of a cow, and both are very different from a pig; and thus, a drug product may be absorbed and metabolized very differently in each species.

The vast majority of animal drugs are used in dilute and variable mixtures that also affect both the bioavailability and potentially unsafe residues.

As a matter of fact, FDA's own bioequivalent study guidelines which have been issued state that a residue depletion study is the preferable manner of establishing that a generic product meets human food safety requirements of posttreatment withdrawal period or tolerance limits.

Based on these concerns and FDA's current requirements S. 2407 should require the generic animal drug sponsor to establish his product's bioequivalence in each major class of animals in which the generic sponsor seeks approval. At a minimum, we believe these four classes should be the ruminant—that is, the cattle and sheep—swine; poultry, including chickens, turkeys, ducks, and so forth; and nonfood species.

Similarly, AHI believes that S. 2407 should be amended to require the sponsors of generic animal drugs to demonstrate that residues of their products are diminished at the same rate and in each approved species as those of the pioneer product.

AHI advocates several other modifications to title I of S. 2407, which are covered in our detailed statement.

I would like now to briefly address patent term restoration for animal drugs and biologics.

At the outset of this brief statement, we explained the principal ways in which animal drugs are different from human use drugs. As written, title II of S. 2407 does not take these differences into account, and merely injects animal health products into the already enacted human drug patent term restoration process.

In brief, these are the changes we propose to title II and the underlying rationale.

S. 2407 would authorize PTR only for the first commercial marketing or use of the product after the regulatory review period. Often, the first commercial marketing of a new animal drug is for use in a nonfood species, because use in nonfood species generally entails relatively uncomplicated FDA requirements and thus a relatively short regulatory review period.

However, when the sponsor proceeds with the development of the complex and costly data necessary to market the same drug for use in a food-producing species, taking far longer to obtain FDA approval, he cannot seek PTR for the patent time lost while awaiting that second or subsequent marketing approval.

If I could leave the text for a moment and just comment on this, in human health when a new use is developed for a human health drug in man in general, a second patent can be filed. When a patent is filed on an animal health drug for feed efficiency or weight gain or for removal of worms in an animal, the patent originally reads covering almost all the species of animals. So that there is not a new use pattern that becomes operative.

While I recognize the human bill itself only allows one NCE, the difference being that new use patents can be filed on a human health product but they cannot be filed on an animal health product, since they are covered in the original patent.

S. 2407 should be modified to allow PTR extensions based on the regulatory review periods involved in food animal uses of pioneer animal drugs, since this is the major economic reason for developing the product.

In the long and arduous process leading up to enactment of the Drug Price Competition Act, many compromises and accommodations were agreed to by the various parties involved. AHI was not one of these parties.

One of those compromises resulted in the provision that only part of the investigational phase of product development could be included in the regulatory review period used to determine the allowable length of patent term restoration.

Due to the need to do both—studies analagous to food additive studies, as well as studies on safety and efficacy in target species, this limitation is entirely inequitable with reference to new animal drugs and would seriously impede the new product R&D incentive that PTR legislation is designed to provide.

In this summary statement, I have only touched upon the highly complex and little-understood issues involved in this legislation.

Thank you again for the opportunity to present our views on this legislation. AHI will be happy to work with your committee in any way you deem appropriate to perfect this legislation, and we will be pleased to respond to any questions you may have.

Before that, I would like to turn to Dr. Sieck, who has collected some fairly recent data on some products that might speak to this issue just a little bit more.

[The prepared statement of Dr. Gillin follows:]

STATEMENT OF THE
ANIMAL HEALTH INSTITUTE
TO THE COMMITTEE ON LABOR & HUMAN RESOURCES
UNITED STATES SENATE
ON S. 2407, THE "ANIMAL DRUG AMENDMENTS
AND PATENT TERM RESTORATION ACT OF 1986"

July 18, 1986

Mr. Chairman and members of the Committee, I am Dr. James Gillin, president of the MSD AGVET Division of Merck & Company and chairman-elect of the Animal Health Institute (AHI). I am accompanied by AHI's General Counsel, Mr. Eugene I. Lambert of the law firm of Covington & Burling, and Dr. Robert F. Sieck, Agricultural Analytical Chemistry Division, Eli Lilly and Company.

AHI is the national trade association whose 52 member companies are the major manufacturers of the animal health products -- feed additives, veterinary drugs, and biologics -- in the United States. To the best of our knowledge, AHI is the only association of such manufacturers, and our member firms, large and small, produce a broad variety of animal health products, both brand name and generic.

We appreciate the opportunity to testify today to discuss the issues of abbreviated new animal drug applications and patent term restoration for animal health products. We recognize that the members of this Committee dealt with somewhat similar issues in the human drug PTR/generic legislation in 1984 (P.L. 98-417). The focus of our testimony today will be to highlight the differences between human use drugs and animal drugs and to demonstrate the need

for different legislative approaches for both abbreviated approvals and patent term restoration for animal health products.

The differences between human and animal use drugs are based on two principal factors. First, an animal drug can be and frequently is used in more than one species. Separate testing is required to obtain approval for each major species based on a presumption that different species can absorb the drug at different rates and they can react differently. Both bioavailability and withdrawal time -- the time it takes the drug to sufficiently leave the animal to assure human food safety -- can differ greatly between species. The fact that the same drug requires separate approval for each species also affects the effective patent life of the product. The second factor is that the reason for using animal use drugs differs greatly from that for using human use drugs. Human drugs are prescribed at exact doses for the treatment of specific illnesses on an individual patient basis. Most animal drugs are administered to food animals to prevent disease and improve growth on a herd or flock basis, and the most common method of administration is to mix the drug in the water or feed. Profitability is the most significant factor in deciding whether to use an animal drug: Is it a cost-effective investment for the livestock producer? In addition, the sponsor of a new drug for food animals generally faces a substantially smaller potential market for a new product than does the sponsor of a human use drug.

These differences explain the drastically different health and economic considerations in the testing and marketing of human use drugs and animal health products. They explain why the formula used to restore patent term for human use drugs does not provide equity when used for animal drugs. Multiple species use and use patterns for animal drugs also explain why a single bioequivalency test in one species (mankind) ordinarily is acceptable to establish the safety of human generic drugs, but frequently cannot provide adequate information about bioequivalency and therefore human food or animal safety in other species.

ISSUES IN THE ABBREVIATED APPROVAL OF ANIMAL DRUGS

In general, we believe S. 2407 with some changes, would provide a sound and workable system in the abbreviated approval title. As is evident from the following comments, we have only a few points of major concern with Title I.

We note at the outset that the underlying scientific issues, primarily of food safety, are complex and have proved difficult even for FDA to resolve. Nevertheless, we all must recognize that the underlying objective -- assuring the continued safety of the human food supply -- is too important to be compromised.

1. Bioequivalence of the generic product to the pioneer

The 1984 human use drug PTR/generic amendments (P.L. 98-417) require that the sponsor of a generic drug product

demonstrate through tests of blood-level concentrations that the active ingredient of the generic is equivalent to the pioneer. The same concept is, of course, applicable for animals drugs, but it is much more complicated.

A pioneer animal drug product is often approved in more that one species. To obtain each approval in a major species, the pioneer must satisfactorily demonstrate safety in each species. Whether a blood-level test showing that a generic product is bioequivalent to a pioneer in one animal species (cattle, for example), tells you anything about bioequivalence in a second species (particularly in one as physiologically different as poultry), is of far more than academic concern. In the limited situations where a product is in a highly purified form and absolutely equivalent chemically, our scientists tell us that it is reasonable to extrapolate evidence of bioequivalence from one species to others. This could be the case with an injectable drug product.

With the vast majority of animal drugs, however, there are additional steps involved in the preparation of the final product. At each step, factors may change the equivalence of the new formulation to the reference formulation, and there is less certainty about the bioequivalence of the product. These factors include different sources of supply of the active and inactive ingredients and different manufacturing processes. Thus, more testing is needed to assure that it is bioequivalent to a reference product with respect to safety

and efficacy. In a feed-form drug, for instance, the inactive ingredients may be 70% or 80% of the product by weight as the product is sold to the end user. The rate of solubility, particle size, and pH of the active ingredients, and similar issues for the vastly larger amount of inactive ingredients, all become more significant. Variations in any of these elements can result in substantial variance in the bioavailability of the active ingredient when you move from one species to another.

In addition to the issue of extrapolating bioequivalence data from one species to another, there needs to be consideration of what "bioequivalence" means in the context of drugs for food animals. The criteria, experimental design and the statistical analysis of bioequivalency studies to assess the equivalence of a pioneer and a generic animal drug product must be very different from that employed for human drugs. This is because the evaluation of drug residues in food producing animals changes the focus used in testing bioequivalence. For human drugs, the major issue in bioequivalence testing is drug efficacy. For food animal drugs, efficacy is obviously important also, but a primary concern has to be drug safety with respect to the food derived from the treated animal.

The bioavailability studies in humans emphasize the need to compare the area under the blood-level curve to assure comparable doses. In contrast, interest in animal drug residue behavior requires primarily a comparison of the <u>shape</u>

of the curve, which gives a clue of retention and excretion. Furthermore, for human drugs, the "more bioavailable" generic product has been perceived by FDA to be a better formulation of the drug, but the "more bioavailable" animal drug product, although it may have some therapeutic advantages over the reference product, could have a very different drug residue depletion behavior. Thus, any legislation providing for abbreviated new animal drug applications should provide that the primary emphasis of bioequivalency should be on equivalency of human food safety aspects and secondarily on efficacy and safety to the target animal.

2. Depletion of residues of the generic product

A primary requirement with regard to animal drugs is that no unsafe drug residue remains in the food derived from treated animals. This is obviously unique to animal drugs.

To provide such an assurance, the sponsor of a pioneer product for food animals must do extensive drug metabolism and toxicity studies of the drug product. If these tests raise any concern about the safety of food derived from animals administered the drug, additional testing must be done to learn the rate of depletion of drug residues from the edible tissues of the animal. At the point in time it can be shown that there are no safety issues with respect to drug residues, a "withdrawal" period is established, and meat, milk, or eggs from the animals cannot be used for human food

unless the drug has been withdrawn from the animals for the specified period of time.

In July, 1985 FDA's Center for Veterinary Medicine published, after significant opportunity for scientific and public comment, a guideline on testing for drug sponsors desiring to produce generic copies of already approved pre-1962 drugs. This "Bioequivalence Study Guideline" describes the type of testing a generic product sponsor needs to conduct to assure the safety of human food derived from animals receiving a generic product. In the guideline, FDA states that "A residue depletion study is the preferable manner of establishing the post treatment withdrawal period for products used in food-producing animals because this study provides a direct measure of the withdrawal period." The guideline then states that, "under certain circumstances, the sponsor may conduct a bioequivalence study in lieu of the depletion study." But the bioequivalence testing must be extensive enough to provide "the time at which there is 95% confidence that 99% of the animals have tissue residues at or below the tolerance limit established for that tissue(s)."

We believe that these principles should be incorporated into the legislation. Unfortunately there is no guarantee under S. 2407 that these principles will be followed by FDA, because of the degree of discretion left to FDA in implementing the procedures. Indeed, S. 2407 seems to create the presumption that a single bioequivalence test will be the rule, and any additional testing will be the exception. We

believe the agency needs clearer congressional direction for standard setting. Moreover, in light of the agency's limited resources, we believe it is a serious disservice to create a system that places any burden on the agency to justify why additional testing is necessary.

In contrast to the FDA guidelines, S. 2407 contains substantially less explicit requirements for the approval of a generic copy of a post-1962 animal drug. Extrapolation of the results of bioequivalence testing from one species to another could become the rule, not the exception as it is in FDA's guideline. Tissue residue testing to determine appropriate withdrawal times prior to marketing could become the exception rather than the preferred approach as it is in the guideline.

What would be FDA's interpretation of this congressional approach? Would FDA conclude that its present guideline should be withdrawn and replaced with one that requires less testing to assure bioequivalence and proper residue depletion? Clearly, there should be no relaxation of these human food safety standards. The interests of government, industry, animal agriculture and the consumer would be ill-served by such an interpretation.

There should be more explicit testing standards in S. 2407, to assure that FDA continues to observe the principles it follows today. The principles enunciated in the Bioequivalence Study Guideline apply to new applications for generic copies of pre-1962 drugs and supplemental

applications for post-1962 drugs. They should also apply to post-1962 generic applications.

The United States has the safest as well as the lowest cost food supply in the world. Our industry is geared to operating in an environment designed to maintain those standards, and we do not want to see them diminished. Our customers, the nation's livestock and poultry producers, are determined to continue to improve the quality and safety of their products. We market our animal health products to help them achieve that goal.

Furthermore, the legislation should require firms intending to conduct bioequivalency studies in food animals to notify FDA of the fact, in order to assure that all such animals are identified and handled in a manner consistent with human food safety.

3. Assurance of a reasonable period of exclusive marketing

S. 2407 would provide the sponsors of pioneer drug products with a period of "exclusive marketing," i.e., a period following approval of the pioneer product in which FDA cannot approve a generic copy. This is an important incentive to the research-intensive drug manufacturer, because there must be a reasonable expectation of a period in which the massive investment in the development of a new product can be recouped.

While we strongly support the concept of exclusive marketing periods, we believe the provisions in S. 2407 must be changed to reflect the realities of the animal drug industry, rather than reflecting the human drug industry experience. Once again, the issue is the use of products in more than one species.

When the pioneer drug sponsor seeks approval of a product in an additional species, the testing and evaluation must, to a large extent, begin again from scratch.

Most significantly, if the first approval for an animal drug was for a nonfood species, as is frequently the situation, the testing required for the first food species will be much, much greater. This is qualitatively and quantitatively much different from adding a new claim for a product in the same species.

Let us illustrate the dilemma posed for the animal health product industry by the current provisions of S. 2407. The bill would treat the approval of a drug for use in cattle which already had an approval in dogs the same as a supplemental approval for a new disease claim in dogs. This does not reflect the reality of the time and expense required to secure that approval for cattle. For instance, a recent survey conducted for AHI by the independent accounting firm of Ernst & Whinney showed that the average research and development cost of a new anthelmintic (wormer) for use in beef cattle would be $16 million and require approximately eight years from discovery to final FDA approval. A similar

product to treat worms in a dog would cost $4 million to $6 million and take four to six years from discovery to FDA approval. These figures apply whether this is a first approval or second or third. The additional time and expense reflect the testing required to demonstrate human food safety and effectiveness of the drug in an entirely different animal species. There is a clear need for an exclusive marketing period which is comparable to the period for the first approval.

ISSUES IN PATENT TERM RESTORATION FOR ANIMAL DRUGS AND VETERINARY BIOLOGICS

As previously mentioned, the need to obtain a separate approval (and to do additional testing) to market an animal drug for each different major species significantly reduces the effective patent term for the drug. Thus, substituting the phrase "animal drug" for "human drug" in the formula used in the 1984 legislation to restore patent loss for human drugs cannot restore an effective patent term for animal drugs.

The 17-year span of patent protection was established by Congress in 1861, and that same patent duration remains in place today. Manufacturers of animal health and nutrition products have found, however, that in reality, usable patent protection exists for much less than 17 years. A substantial amount of this patent protection loss is due to the exceedingly complex systems U.S. regulatory agencies have

evolved for pre-market approval of animal health products. New animal drugs cannot be marketed without the prior approval of the Food and Drug Administration; animal biologics must be licensed by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service before they can be marketed. These systems of pre-market approval have provided our nation with a wide array of animal health products with high s andards of safety and effectiveness. But the systems are necessarily time consuming, and, as our knowledge has grown in the biological sciences, statutory and regulatory requirements have expanded. These requirements have become so costly and time-consuming that they diminish the incentives to develop new products.

Effective Patent Life is Decreasing

Effective patent-life loss has come about with the expansion of drug approval requirements, starting with the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act). These amendments spawned massive requirements for efficacy data for both human and animal drugs. Patent term losses have become even more extensive over the past decade. In 1973, FDA proposed new scientific standards for the review of potentially carcinogenic new animal drugs, implementing the 1958 Delaney Clause and the 1962 DES Exception, both of which were codified in the 1968 Animal Drug Amendments. This proposal, commonly called the "sensitivity of method" standard (SOM),

has been formally revised twice, and has yet, more than a dozen years later, to be finalized. Nevertheless, the proposed regulation has been employed as the scientific standard of review since its publication. The effect has been dramatically increased review times for new animal drug applications (NADAs) for food-producing animals. (For a decade, the SOM requirements were so stringent that no, or only 1 or 2, NADAs for new chemical entities for use in food-producing animals were approved annually.)

Numerous other causes have been identified by our industry as contributing to the length of the approval process and thus to the diminution of effective patent life. The excessively long periods during which products languish in the regulatory process, especially compared to approval times in nations with comparable regulatory systems, has become known as the U.S. animal drug lag. Since 1980, FDA has taken several steps to reduce the animal drug review time, but substantial reductions simply are not possible under the current system of careful food safety evaluation.

In the summer of 1985, AHI conducted a survey of member companies to determine the lengths of patent time lost on recent approvals of drugs for use in food animals, i.e., approvals since FDA began applying the sensitivity of method rules in 1973, and we received usable responses from 11 members. For approved new products, there was an average loss of patent time due to the regulatory review process of 5 years and 11 months where a composition patent was involved,

but products still awaiting approval had already incurred an average loss of patent term of 7 years and 7 months. When there was a use patent involved, the average loss for approved products was 3 years and 8 months and 6 years and 5 months for products awaiting approval.

These figures on patent life loss on pending products are particularly noteworthy. Several of the products involved were, of course, recent filings and had lost less then two years of patent term; however, 17 of the total of 31 covered by product or use patents had lost more than seven years of patent life as of June, 1985 with some more loss certain. This suggests an alarming trend in regulatory review times, and we anticipate the average loss of patent time will grow.

Societal Benefits of this Legislation

In addition to the equitable aspects of patent term restoration legislation, the longterm benefits to society should not be overlooked. Animal vaccines and other biologics and dosage-form pharmaceuticals help livestock and poultry producers minimize disease losses. Animal scientists estimate that the livestock industry suffers a 20% loss annually from diseases; obviously, more research needs to be done, but great advances have been made, as evidenced by losses of more than 50% per year in some less-developed countries.

Animal feed additives are of great economic importance to livestock producers. These products give producers the capability to obtain maximum efficiency from the resources available. Thus, they are a major factor in making abundant supplies of meat and poultry products available to consumers at reasonable prices.

The public health aspects of animal disease prevention cannot be ignored, either. There are over 150 zoonotic diseases, i.e., animal diseases transmissible to man. Some, such as rabies, can be controlled by animal vaccination; others, such as brucellosis, still evade eradication.

These are serious animal disease problems which threaten the economic lives of livestock producers and pose risks to human health. Much more needs to be done to develop treatments for viral diseases and the difficult-to-treat bacterial diseases, such as brucellosis. The animal health industry is poised to attack now-incurable diseases and to find preventions or cures that are safer and more effective than the products now available.

The animal health products industry is heavily committed to working toward these goals. Based on a survey of 1985 sales, the Animal Health Institute estimates that domestic net sales of animal health products totalled just under $2 billion. The survey also provides the estimate that in 1985 AHI firms spent over $296 million on research and development of animal health products sold or intended to be sold in the United States. AHI estimates that about 91 percent of the

R&D is "innovative" research aimed at development of new products, with the remainder being to demonstrate the continued safety and effectiveness of already-approved products.

Despite the significant losses of effective patent life, animal health product manufacturers have continued to invest heavily in new products. However, innovation has clearly suffered. As a practical matter, the drug developer must assume that a newly-discovered product will have at most 10 years of patent-derived marketing protection. R&D can be devoted only to a product with a potential market sufficiently large to recoup the investment in 10 years, instead of the 17 years that innovators in other fields enjoy. Current estimates from another AHI study indicate that the directly attributable R&D costs for a new drug for a food-producing animal are in the range of $14 to $16 million. The market must be large to recover such an investment and yield a profit in a short time. Furthermore, these figures do not reflect the entire investment to be recovered -- they do not include the expenditures on possible products that do not work out. Another four or five years of patent protection would allow the recovery of an investment with a product of significantly lesser volume. If the current situation is unchanged, the incentive to conduct R&D aimed at products for less common diseases or diseases in the less common species will continue to diminish.

S. 2407 would not provide adequate incentives for the development of the animal health products

The preceding data suggest that the patent time lost to the regulatory review process is similar for human and animal drugs. But that should not end the inquiry into the adequacy of the legislation for the animal drug industry.

P.L. 98-417 added Sec. 156 to the patent law, which authorizes restoration only for the "first commercial marketing or use of the product after such regulatory review period." S. 2407 would simply add animal drugs to Sec. 156, providing PTR identical to that for human drugs. This is grossly inequitable for animal drugs. In the normal course of animal drug development, the sponsor seeks approval for marketing for several species. The approval is usually obtained for a nonfood animal use first, e.g., for dogs. This is the regulatory review that would be the basis of patent term restoration if the provisions of Sec. 156 were applied.

However, generally much more extensive testing time and money are expended in the development and approval of both first and subsequent approvals for use of a product in food animals. There needs to be a means in the patent laws to recognize that the background work for the "first commercial marketing" may not be the truly burdensome load.

Furthermore, Sec. 156 has several intermediate "caps" which limit the amount of the time of the patent extension. These caps include a maximum patent term of 14 years from the

date the NDA received FDA approval and allowance of only one-half the regulatory review time involved with the investigational stage of product development. These "caps" appear to be essentially arbitrary limitations imposed by the political requirements of the various groups affected by the human use drug legislation. We do not believe that such caps are relevant to the animal drug and biologics industry; the fundamental principle of a maximum patent extension of five years should be sufficient.

Economic influences on the sale and use of animal drugs

Some animal drugs are used in much the same manner as human drugs, i.e., dosage-form drugs are given to individual patients following a specific diagnosis by a medical practitioner. This is obviously the case for "companion" animals, e.g., dogs, cats, and horses.

As discussed earlier, most animal drugs are used in an entirely different context, however. They are used to prevent or mitigate disease in a herd or flock. The animals' owners, whether they be feedlot operators in Oklahoma or broiler producers in South Carolina, want to preserve their animals' health.

Cost is the controlling factor for the livestock or poultry producer. The market prices for his product are so competitive that he has to be constantly aware of the profitability of each of his "inputs." The costs for feed and medications are two of the major variable costs of

production. When considering whether to use a new vaccine or drug, the farmer has to decide whether it will return a profit. For example, will savings on other inputs (such as feed) more than cover the cost of using a growth-promoting drug? If not, there is no reason to use the product.

It is this economic environment in which any new drug for food animals is marketed. To be successful, a new product must be at least as cost effective as existing products. No matter how innovative from a medical standpoint; no matter how many years and how much money were devoted to developing this product, the product must be cost effective for the livestock producer.

In the marketing of dosage-form, single-patient therapeutic agents, the economic pressures are not quite so strong. Whether the patient is a person or a pet, the intrinsic value of the patient's good health is high; this is simply not the case with the food-producing animals, where individual animals are culled for the betterment of the herd or flock.

For instance, a new vaccine for human use that is safer and more effective will have wide acceptance, even at a substantial premium. The reduced risk of adverse reactions and the increased degree of protective immunity will far outweigh an additional cost of a few dollars per dose. But the owner of 1,000 hogs must judge a new vaccine differently. Will the reduced productivity loss from fewer adverse

reactions be sufficient to justify the extra $2,000 in vaccine costs?

As a result, the manufacturer of a food animal drug must price to the economic conditions of his customers, not to the research and development costs that went into the product. The product's uniqueness from a biochemistry standpoint counts for little if its cost is out of line with the return a livestock producer can hope to achieve with its use, or if it must compete with existing products with similar use claims.

Recommendations for changes in S. 2407

Patent Term Restoration for pioneer animal health products is long overdue. Animal drug PTR has been endorsed repeatedly by the Judiciary Committees of the Senate and the House of Representatives dating back to the 97th Congress. As a matter of fact, the Senate passed a bill (S. 255) providing animal drug PTR five years ago, on July 10, 1981, and that more generous bill would have allowed maximum patent term extensions of seven years, as compared with the current bills' five-year maximums.

In the 98th Congress, animal health products were covered by the original two-title bills providing for generic human drug approvals along with PTR for all patented drugs, human and animal. Animal health products were deleted from those bills at the industry's request, prior to the 1984 enactment of P.L. 98-417.

In this 99th Congress, the Agricultural Patent Reform Act, S. 1093, introduced by Sen. Mathias last year, has been approved by the Senate Judiciary Subcommittee on Patents, Trademarks, and Copyrights. This bill is specifically tailored to the economic conditions and needs of agricultural suppliers who face federal pre-market approval requirements.

Overall, S. 1093 addresses the concerns of the animal health products industry, and we recommend that it be used as the basis for Title II of S. 2407. The "bottom line" of S. 1093 is the same, i.e, up to five years of patent extension to restore time lost in the regulatory review process. But the formula for determining regulatory review time more appropriately reflects the regulatory process for animal drugs than does the formula in Sec. 156 of the patent law. This is an extremely important consideration in determining whether animal drugs would receive meaningful patent term restoration.

Furthermore, S. 1093 is structured so that regulatory review for the "first commercial use" of an animal drug need not be the review period that really entails the major loss of useful patent life.

Conclusion

We have described the fundamental differences between the development, marketing, and use of animal drugs and human use drugs. In contrast to human use drugs, animal drugs are used in more than one species; they are used primarily to

prevent disease and increase productivity, and they must pose no threat to the human food supply. Furthermore, the vast majority of the sales of animal drugs are to livestock producers who are interested only in products that are priced so that their use will enhance the profitability of the livestock or poultry operation.

We have identified several areas where amendments to S. 2407 are essential, with two goals in mind. First, to assure the continued credibility of the animal drug industry and the wholesomeness and purity of the meat, milk, and poultry products resulting from the use of these animal health products. Second, to provide a means to obtain a fair and equitable return on research investment through patent term restoration which reflects the realities of animal agriculture and the federal approval process for animal health products.

Attached to our statement are two FDA documents which describe the agency's current requirements for the testing of reformulated and generic animal drugs, the "Bioequivalence Study Guideline" and the "Guideline for New Animal Drugs and Food Additives Derived from a Fermentation; Human Food Safety Evaluation."

Once again, AHI appreciates the opportunity to present its views. We would be happy to answer any questions that the members may have, and we look forward to working with the committee in developing appropriate amendments.

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The CHAIRMAN. Dr. Sieck?

Dr. SIECK. Thank you, Senator.

As Commissioner Young has testified, there are data, and the FDA has data, showing that bioequivalence between generic and pioneer products can be very reflective of the efficacy and tissue residue safety for drugs which are used in the animal health industry.

We are very supportive of FDA's given approach to date. The bioequivalency guidelines which were issued in 1985 specified establishment of bioequivalence as an effective approach to take.

They note, however, that in many cases it is not possible to establish bioequivalence, as Dr. Young's example showed, using blood level data, because in many cases in animal drugs, particularly those used in feed, blood levels are not sufficient to measure that. And they cite in those guidelines that in those cases, bioequivalence might have to be established based on efficacy kind of information.

It is very important in those kinds of cases to recognize the difference in the issue of bioequivalence. When you can have the blood level information through bioavailability studies, you can accurately predict in cases of established identicality of drugs, some information about tissue residue. If you cannot measure biological fluids or are operating in the period when there is not steady state, such prediction cannot be made.

Another concern out of our experience which FDA is aware of is the issue of going from species to species. Without data to support that, we think that is a very precarious difference, and we can get into an area of food safety, which is a matter of great concern.

We have an example, one of our products, in which we were evaluating manufacturing parameters, which is used in both cattle and poultry. We discovered in this evaluation a case where there were very small differences which we were not able to accurately determine and set parameters on, wherein the product worked very effectively in cattle, and when given to poultry, the chicken would pick out particles from the product which apparently were a slightly different shape or color and could have adverse drug reaction, issues of target animal safety. And of course, getting larger doses of drug, if the animals had not died, there would have been issues of human food safety in that instance, relative to the poultry meat.

Now, in that case, the issue was a question of the processing. Should that process have been used and an efficacy study run to show bioequivalence in cattle and that data be used as justification for clearance of that product in all species? You could have an issue of target animal safety and a potential issue of human food safety which would not be covered.

It is for these reasons that we think evaluation in each target species is very important and should be maintained.

The CHAIRMAN. Thank you so much.

Let me just ask a few questions here. Dr. Gillin, you spoke out about the importance in the manufacturing process of assuring that approved residue levels are not exceeded. Now, is it not true that there have been improvements in manufacturing as well as other changes in these products—shown by supplementary applications—such that the drug products that your members market

today are not identical to the products originally approved by the Food and Drug Administration?

Is that true?

Dr. GILLIN. Certainly.

The CHAIRMAN. OK. Is it not true that the manufacturers have not routinely been required to repeat the human food safety, efficacy or tissue residue studies for these drug products?

Dr. GILLIN. Not completely, Senator. Depending on the magnitude of the change of the process, we will very often repeat bioequivalence studies and even drug residue studies on a major process change. It is very hard to define what is a major and minor process change, but if the analytical techniques assure us that the bulk product itself is essentially the same, there is seldom necessity to make a change.

But we have, for example, gone to a manufacturer of one of our major products, Nicarbazin, that was used in chickens, and when we have gone to that toll manufacturer, a different manufacturer than Merck & Co., we have completely repeated the bioquivalence studies and the drug residue studies, to assure ourselves, even though the quality standards were the same.

The CHAIRMAN. But when and if the Food and Drug Administration wanted to repeat such studies, it could order them any time it wanted to, couldn't it?

Dr. GILLLIN. I am sorry, I cannot hear you.

The CHAIRMAN. When and if FDA wanted such repeat studies, it could require them if it wanted to.

Dr. GILLIN. It certainly could do that, but we do not feel that the burden should be put on the Food and Drug Administration. They have difficulties enough with a tight budget, to ask them to justify these things. We think the burden of proof should be on the manufacturer.

The CHAIRMAN. OK. But does not S. 2407 authorize FDA to require tissue residue studies; does not this bill require that?

Dr. GILLIN. I do not believe so. I read in it bioequivalence, and the definition of bioequivalence is not really spelled out anywhere.

Mr. Lambert will speak to that.

Mr. LAMBERT. Senator, I think our concern is very much that as we read the bill, it places the burden on FDA of justifying requesting additional studies rather than——.

The CHAIRMAN. If they want to have them, they can request them.

Mr. LAMBERT. Yes, but it seems to me that it raises the question of FDA having to justify to the applicant that such additional studies are needed, rather than the applicant having the burden, as it seems to me the act presently requires every applicant to have, to justify that the data that they have submitted is sufficient to prove that their drug is safe and effective, including human food safety.

We are very concerned that the way the bill is drafted, it shifts that burden and that presumption away from the applicant and onto FDA. And in no other part of the act as far as we know is there this sort of shift where an applicant can come in with one study and then turn to FDA and say, "You prove that something more is needed." And we are concerned that that is how this bill would be read.

The CHAIRMAN. OK. Aren't several generic companies supplying and manufacturing products for your member companies?

Dr. GILLIN. As I mentioned, Nicarbazin, we are buying from a generic manufacturer.

The CHAIRMAN. All right. We appreciate having you here today, Doctor.

Senator Simon, we will turn to you.

Senator SIMON. Thank you.

First, if I may ask about the Animal Health Institute, do you do research, or——

Dr. GILLIN. At the institute, no, sir.

Senator SIMON. You do not. It is just a cooperative endeavor by the various——

Dr. GILLIN. It is a trade organization.

Senator SIMON. All three of you used the term "species." Are we talking about cows, lambs, and so forth, or are we talking about—is Black Angus a separate species from Hereford, or what? This is basic, but I have to get the basics down to understand.

Dr. GILLIN. They are different species as well, but what we are referring to in the species are major differences between a cow, a sheep, a pig, and poultry.

Senator SIMON. OK. So by species, we are not talking about hundreds or thousands of tests that would have to be made?

Dr. GILLIN. Although the Food and Drug Administration has required us in the past, in the case of poultry, to distinguish between breeding flocks, laying flocks, and broilers—surprisingly—but they have not required that in the past on breeds of cattle.

Senator SIMON. Now, you heard my question to the Commissioner on the residue. How would you answer that question?

Dr. GILLIN. Would you repeat it, please, Senator?

Senator SIMON. Yes. The question is can we be sure that there is no residue problem without basically waiting until—in the case of chickens, say, 18 weeks have elapsed to actually test for that residue, or whatever it is in other species.

Dr. GILLIN. I will defer to Dr. Sieck to answer that. I do not believe that we could guarantee it without doing the appropriate bioequivalence and residue studies.

Dr. SIECK. Yes. We think that one has to be very cautious. To answer the question, are there instances where bioequivalency data can accurately reflect what a tissue residue situation would be, the answer is yes. And as the Commissioner showed, in evidences where there are very high-blood levels at steady state, which would be the case with a therapeutic kind of drug, for example, that is an example case.

But where you cannot measure blood levels, which is very often the case in feed-additives, and in feed-additive situations where you have a very complex mixture as the dosage form, it has been our experience with the FDA to be very cautious about that, and we think that caution is very, very appropriate. In particular, where you cannot measure blood levels, as I testified, Senators, we think it is inappropriate based on efficacy tests alone to project the safety of residues, and most certainly to project between species.

Senator SIMON. When you say you think it is inappropriate, have you had actual tests? Do you do testing at your firm?

Dr. SIECK. Yes.

Senator SIMON. And do you have tests that suggest that maybe two and two just do not equal four quite as simply as has been suggested?

Dr. SIECK. Yes, Senator. The example I gave of a situation where, in a cattle feed a product would look safe, but due to peculiarities of how chickens eat that product, may not be safe from both the target animal safety standpoint and from a tissue residue safety standpoint in poultry.

So that kind of judgment, we feel, should be based on data for the specific species and not based on extrapolation.

Senator SIMON. If this were to be amended so that you would require that residue test before you could approve a generic drug, in the case of chickens, how long would you have to wait?

Dr. SIECK. I do not understand the question, Senator.

Senator SIMON. In other words, how much of a delay are we talking about in the effective date of—in other words, I have heard 18 weeks. I do not know whether that is accurate or not.

Dr. SIECK. Oh, OK. The length of a life of a chicken in the broiler industry these days is about eight weeks or less.

Senator SIMON. Eight weeks, OK. So my 18 weeks is only 10 weeks off. All right. Eight weeks. In the case of swine, what are we talking about?

Dr. SIECK. Well, those can run——.

Dr. GILLIN. Well, it is not the life of the animal that is really germane here; it is the withdrawal period that is required from the time you feed the drug until you slaughter the animal for food. And most of those withdrawal periods at the maximum that is really practical for any farmer would be 1 month or 30-day extension. So about the most you are talking about in any species of livestock would be a 30-day test. You would feed the drug, wait 30 days, and then test that the drug really was cleared of the animal.

Senator SIMON. Can you test residue in 30 days?

Dr. GILLIN. Yes.

Dr. SIECK. Yes. These studies, Senator, can be run typically, a complete study to generate the data upon which judgment could be made, can be done in a 2- or 3-month period.

Senator SIMON. So that if we were to amend this to require that residue study, we are not talking about any lengthy delay at all, then, in the effective——

Dr. GILLIN. No. That is correct.

Senator SIMON. OK. Let me ask one other question—again, I am new to this whole field. I notice in your testimony here, Dr. Gillin, you used the phrase "patent term restoration." Does that mean that you want the term of the patent extended for the period of the time you have had to wait for approval of something, or what do you mean by the phrase, "patent term restoration"?

Dr. GILLIN. Yes, that we believe we are losing valuable coverage under a patent for the time that it is sitting in regulatory review, just as in the human health bill, and we would like to see an extension based on the amount of time in that regulatory review period.

Senator SIMON. And how long does that regulatory review period last, generally?

Dr. GILLIN. On a product for a major food animal species, it can run anywhere from 8 to 10 years.

Senator SIMON. OK. I thank you very much.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you so much.

We appreciate you good folks appearing before us today and the efforts you have made. Thanks for coming.

Our third panel is Dr. Sorell Schwartz, professor of pharmacology, Georgetown University School of Medicine.

Dr. Schwartz, we are happy to have you here today with your associate, and we look forward to taking your testimony at this time.

STATEMENT OF DR. SORELL L. SCHWARTZ, PROFESSOR OF PHARMACOLOGY, GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE, ACCOMPANIED BY DR. RICHARD WILSON, PROFESSOR OF PHYSICS, HARVARD UNIVERSITY

Dr. SCHWARTZ. Mr. Chairman, I am Sorell Schwartz. I am professor of pharmacology at Georgetown University School of Medicine. And with me for purposes of aiding and responding to questions is Dr. Richard Wilson, professor of physics at Harvard University.

At the request of pharmaceutical companies through an independent consulting contractor, a panel of scientists was formed to consider the scientific efficacy and safety issues that must be addressed in the development of legislation and regulations permitting the sale and use of generic drugs for animal use.

I have submitted a statement, which I ask be entered into the record. I will summarize it.

I am submitting for entry into the record the report of our panel, of which Dr. Wilson and I are members. The other members are listed in my statement.

I will at this time highlight what we consider the critical issue in this legislation, that is, the matter of human safety.

Though therapeutic equivalence for animal use is an important consideration, as it obviously is for human use of generic drugs, when considering drug products intended for use in animals, it is necessary to consider an additional standard of equivalence. That is the drug residue equivalence in edible tissue.

Our premise is that human safety enters into consideration of animal drug product equivalence. That there is acceptable equivalence in blood levels does not a priori mean equivalence for edible tissue residue.

It is possible for two different drug products to produce therapeutically equivalent blood levels while at the same time giving rise to toxicologically significantly different residues in tissues. This is primarily due to the fact that drugs do not uniformly distribute throughout the body in identical concentrations.

Tissue distribution of drugs or metabolites cannot be predicted solely from studies in which blood levels alone have been monitored. With all due respects to the Commissioner—and I say due respects sincerely—bioequivalence measured just by blood levels is inadequate.

I will summarize by saying that we consider the overriding issue is not therapeutic equivalence, but human safety; that without a requirement for bioequivalence monitoring of tissues, which includes these residue factors, additional risk is encountered where

no additional risk can be justified. And finally, we are not talking about an animal drug. We are talking about a human food additive. And in that respect, we suggest that Congress do what it has always done for food additives, and that is excercise its legislative mandate.

Dr. Wilson and I will be happy to answer any questions that you might have, and we appreciate the opportunity to make this presentation before you.

[The prepared statement of Dr. Schwartz follows:]

STATEMENT OF SORELL L. SCHWARTZ, PH.D.
BEFORE THE SENATE COMMITTEE
ON LABOR AND HUMAN RESOURCES

July 18, 1986

Mr. Chairman:

My name is Sorell L. Schwartz. I am professor of Pharmacology at Georgetown University School of Medicine. At the request of several pharmaceutical companies, and through an independent contractor, a panel of scientists was formed to consider the scientific efficacy and safety issues that must be addressed in the development of legislation and regulation permitting the sale and use of generic drugs for animal use.

The members of the panel, with interest in risk management, regulatory posture, animal husbandry, processing and analyses, and pharmacologic, toxicologic and pharmacokinetic properties of materials, were, in addition to myself:

Neal L. Benowitz, M.D., Associate Professor in Residence, San Francisco General Hospital Medical Center, Departments of Medicine and Psychiatry, University of California, San Francisco

Frederick W. Oehme, D.V.M., Ph.D., Professor, Comparative Toxicology Laboratory, Kansas State University

Joseph V. Rodricks, Ph.D., Principal, Environ Corporation

Richard Wilson, D.Phil, Mallinckrodt Professor of Physics, Department of Physics, Harvard University

In considering the requirements for an abbreviated process for approval of generic animal drugs, the drug products must be treated both as drugs and as additives to the food chain. It is therefore necessary that data be provided to show: (1) the biological equivalence and (2) both quantitative and qualitative biological equivalency of residues of the generic drug and its metabolites in the food chain to pioneer drugs. Data are also needed that show that the methods used in production and assay of the generic drug both during production and during inspection of drug-containing foodstuffs are reliable and dependable.

The report of our panel in which these matters are discussed in detail has been submitted to your staff, and I would request that it be made a part of the record.

I will take this time to highlight what we consider a crucial issue -- that dealing with human safety.

Three definitions of equivalence are generally employed for human drug products:

Pharmaceutical equivalents - Drug products that contain the identical active ingredients in identical amounts in identical dosage forms and that meet USP disintegration and dissolution standards.

Biological equivalents - Pharmaceutical equivalents that will provide essentially identical biological availability as measured by pharmacokinetic parameters.

Therapeutic equivalents - Pharmaceutical equivalents that will give essentially the same therapeutic response when administered in the same dose.

Biological equivalents are therapeutic equivalents, but the reverse is not necessarily true. That is, therapeutic equivalents need not be exact biological equivalents. They have to be close enough in bioavailability that the blood levels are maintained within the therapeutic range for an acceptable time course. It is important to note that the basis for biological equivalence refers to achieving and maintaining therapeutically acceptable blood levels. When considering drug products intended for use in animals, it is necessary to consider an additional standards of equivalence, i.e., drug residue equivalence in edible tissue.

The premise is that human food safety enters into the consideration of animal drug product equivalence. That there is acceptable equivalence in blood levels does not a priori mean equivalence for edible-tissue residue. It is possible for two different drug products to produce therapeutically equivalent blood levels while at the same time giving rise to a toxicologically significant difference in edible-tissue residues. This occurs because most drugs do not distribute uniformly throughout the body. Consider, for example, that the ratio between skeletal muscle and blood for a certain drug is 10. That is, there is ten times the concentration of the drug in skeletal muscle than in blood. A 20 per cent difference in blood levels (generally considered therapeutically acceptable) would, in a simplified example, result in a 20 per cent difference in edible-tissue (skeletal muscle) levels. However, the absolute difference in muscle levels would be ten times that of the blood. This could result in meeting or not meeting residue tolerance standards.

In summary, tissue distribution of drugs or metabolites cannot be predicted from bioavailability studies. Recognizing possible differences in the physical or chemical characteristics of the drug or the formulations thereof, experimental data must be collected to show that tissue residues of generic drugs are equal, in terms of both concentration and depletion, to those permitted for the pioneer. Without data from such studies no application for a replacement interchangeable with the pioneer can be complete.

Mr. Chairman, thank you for allowing me to make my presentation. I will be happy to answer any questions you or other members of the committee may have at this time.

The CHAIRMAN. Well, thank you. We appreciate having your testimony.

Your paper suggests that using bioequivalent studies alone makes it impossible to produce a generic animal drug that meets the withdrawal period established on the basis of the pioneer product.

Let me just ask this. Do you have any evidence that the generic animal drugs already approved by FDA without tissue residue studies do not meet the appropriate tolerances?

Dr. SCHWARTZ. No, we do not have any evidence. What we do have is a very firm theoretical and experimental data base to show that while very small changes in drug absorption rates from the gastrointestinal tract may still result in therapeutically equivalent blood levels—blood levels that are within about 20 percent of each other—there can be large variations in tissue levels. This is because the drug is not in a steady-state distribution as is often presumed.

I can give you an example. Suppose we find that with a particular drug, after it distributes in the body, it is concentrated ten times more in the muscle, the edible portion, than it is in the blood—not an uncommon occurrence. As I said, drugs do not uniformly distribute in uniform concentrations.

A 20 percent variation in the blood level may have no therapeutic significance at all, and therefore the drugs would be therapeutically equivalent. But that 20-percent difference in muscle level is quantitatively magnified 10 times, because of this concentration factor, and therefore what may not be therapeutically different may very well be toxicologically different.

This is not anything other than what is very well known as basic principles of pharmacokinetics. The problem is getting to and measuring this material. And at this particular time, the only way we can demonstrate these effects is to actually measure the tissue itself.

The CHAIRMAN. Thank you.

Senator Simon.

Senator SIMON. Thank you very much.

I recognize that you have done this at the request of the pharmaceutical companies. And there is nothing wrong with that. But your testimony here, we have to consider the public interest and protection, which obviously, you are concerned about, too.

You heard the questions I addressed to the previous witnesses. I think you have answered it, but let me pose it again. The residue problem is one that we ought to take a look at—I think you have answered that part of it.

Dr. SCHWARTZ. Unequivocally, yes.

Senator SIMON. OK. The second question is what kind of a timelag are we talking about? You have heard the last witness say it is a relatively short timelag, if we say let us take a look at this residue problem.

Dr. SCHWARTZ. I think that is part of the problem. It really depends upon the drug. You cannot say categorically what the timelag would be. It depends really upon the properties of the drug. And that, in fact, would have to be determined. In other words, it

is the studies, the blood level and tissue studies, which would actually determine what type of timelag you would have.

Senator SIMON. When they mentioned 30 days, is that far too short; is that longer than it should be?

Dr. SCHWARTZ. Well, for most situations, 30 days would certainly fall within a degree of expectation of being adequate. But I still feel it should be verified.

Senator SIMON. OK. But if this were amended so in most cases, it would be a 30-day delay.

Dr. SCHWARTZ. If I am interpreting your question correctly as to the time to take to get the data, the answer would be yes.

Senator SIMON. OK—assuming that it takes some additional time to set it up and everything. What is the longest that that would take—and again, I am getting into a field I know nothing about—but how long would be the longest test that would be required?

Dr. SCHWARTZ. Well, I could give you examples of environmental chemicals where we are dealing with years. But for most drugs we are talking about, 30 days is certainly realistic. I cannot see very many that would go beyond that, and I think most would be shorter.

Senator SIMON. So that if we were to add such an amendment, we would be protecting the public in the case of most drugs, and not delaying the effective date of this legislation unreasonably?

Dr. SCHWARTZ. With respect to the time to do the studies, yes. You are not talking about studies that take years, like bioassays for carcinogens or something like that. This is strictly a short-term experiment.

Senator SIMON. Professor Wilson, do you wish to add anything?

Dr. WILSON. I would just like to add that if one leaves solely the blood equivalence as the test for human safety, one is adding an extra uncertainty in the whole chain of calculations, and the whole of food additives, Congress has traditionally demanded that one be exceptionally safe, and FDA following this has set a set of regulations which demand extreme safety and they have, whenever there is uncertainty, demanded that you be extremely pessimistic. You are now introducing an additional uncertainty if you accept blood tests without going through the actual residue equivalents. And unless one adds to the bill, one is going to treat that extremely pessimistically and not regard them as equal and put in an extra safety, then one is not then protecting the public as well as has been done before in food additives.

Senator SIMON. Let me play the devil's advocate just for a moment. Some people say well, if you are here representing the pharmaceutical companies, you simply want to delay the effective date so the pharmaceutical companies can have more profits. How do you respond?

Dr. SCHWARTZ. If that is the reason, they certainly have not told me about it. We were asked to examine the problem and make recommendations. We have not been privy to any legislative strategy sessions, if there have been any.

As far as our own motives there is no disguised agenda.

Senator SIMON. And you did not start off this whole thing with some predisposed——

Dr. SCHWARTZ. Try to obfuscate matters under legislative scrutiny? No.

Senator SIMON. All right.

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator.

Thank you, Dr. Schwartz. We appreciate your appearing today, both of you.

Our next witness will be Mr. William Haddad, who is chairman of the Generic Pharmaceutical Industry Association.

Bill, we are happy to welcome you before the committee. We recognize the paramount role you played in the Patent Term ANDA bill, and we are looking forward to hearing your testimony today.

You might want to focus on some of the past testimony as well.

STATEMENT OF WILLIAM F. HADDAD, CHAIRMAN, GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION, NEW YORK, NY

Mr. HADDAD. Thank you. I will enclose a full statement for the record.

The CHAIRMAN. Without objection, we will put all full statements in the record.

Mr. HADDAD. My name is William Haddad. I am chairman of the Generic Pharmaceutical Industry Association. Our members manufacture and distribute approximately 85 percent of the human generic drugs sold in this country. I am also vice chairman of Danbury Pharmacal, a generic drug company, and a director of Schein Pharmaceutical.

GPIA participated actively in the discussions of the Drug Price Competition and Patent Restoration Act of 1984. As Senator Hatch and Congressman Waxman have reported to their colleagues, consumers and governments are already reaping economic benefits of that legislation.

Savings of almost $1 billion a year result from that historic legislation. Your legislation, Senator Hatch, has a human side, too, which is often hidden in the statistics.

Poor Americans who could not afford to pay for prescription drugs and had to sacrifice food, housing, or heat, can now have both. They may not know how this happened, but those of us who participated in the process realize that it was your tireless, even-handed, and often politically courageous personal involvement which made the difference. We thank you.

When I was reviewing the data for this presentation, my journalistic side kept struggling for a simple phrase to characterize and summarize what you and Congressman Waxman are trying to do. The best label seems to be "Son of Hatch-Waxman," for that is what this is all about—precisely.

In 1984, you were presented with a non sequitur. Drugs whose patents had expired still maintained their marketplace monopoly because FDA did not have a process to approve drugs which entered the marketplace after 1962. There was an active and effective process in place for drugs which entered the market prior to 1962.

To confuse the Congress, the brand name industry dressed up the wolf of economic truth in hired academic garments to be worn by scientific sheep.

You are presented with the same non sequitur with regard to animal drugs. By this legislation you will remove the governmental barriers to competition in the marketplace and the economic gains will quickly flow to farmers, ranchers, breeders, and animal lovers.

There is no logic and less science which should permit a patent-holder, no matter how many academic sheep he hires, to extend his marketplace monopoly beyond the life of a patent. And the Congress should not subject a neutral protector of the public health, the Food and Drug Administration, to twist its processes to accommodate a political reality disguised as a technical condition.

The hard facts to support your legislation are readily available. For veterinary drugs which entered the marketplace prior to 1962, there is a process of sorts in place. There is no process in place to approve post-1962 drugs. According to FDA estimates, 150 to 175 new chemical or molecular entities have been approved for veterinary use since 1962. Because many of the NCE's are approved for use in more than one species, the total number of post-1962 NDA's approved is around 445. Only a handful of these have competition, though patents have expired. That must sound familiar to you, Senator.

The reason for this paucity of multiple-source post-1962 veterinary drugs may sound familiar to members of the committee: the costs of unnecessarily reinventing the wheel, the costs of duplicating tests to demonstrate safety and effectiveness are prohibitive. As you decided in 1984, and as Commissioner Young has testified today, these tests are unnecessary and may be unethical.

What are the economic consequences of this legislation? Farmers will pay half the price for their veterinary products; so will animal lovers. And others. As you know, in the human side, when the first generic enters, the price of the brand name is cut in half. When you have three or four competitors, it drops to 29 percent. The same thing will happen in the veterinary field as soon as competition is permitted, for all patent drugs.

Let me put some facts behind that statement. A brand name company first obtained approval of the antibiotic gentamicin sulfate for dogs in 1967 and now holds an approval for cats and horses as well. It held that monopoly until 2 months ago, when a generic came into the field by duplicating the safety and effectiveness standards. The difference now is $31 for the brand, and $16.40 for the generic. I will guarantee you that price will be cut in half and in half again when you have more generic competition.

And for the record, I will give you other examples of the economic consequences.

In addition to the equity and economic rationale for the legislation, there are significant public purposes to be served. The marketplace reality now—and I am summarizing this—is that veterinarians use generic human drugs rather than veterinary brand name products, and this creates problems, or could create problems.

Also, this legislation will decrease the number of animals slaughtered to reach certain scientific conclusions.

Finally, we concur with the proposed FDA approval requirements for veterinary drugs. We were there before. There were 8,000 versions, generic versions, of 170 brand name products ap-

proved by the FDA without, in 20 years, a single therapeutic failure—not one. Now, that is a track record to go against theoretical hypothesis.

The fact is, the same thing has happened in the animal field, as you have indicated. There is no evidence that in pre-1962 drugs, there has been any difference in the generic versus the brand name.

I wish Senator Simon were still here, because he was one of our allies on the House side with Albert Gore, Henry Waxman, Barney Frank, and Charlie Rangel, when we first started this campaign.

There is no difference between a brand name and a generic drug. They are identical, and they can be proven identical.

I will be glad to answer any questions you have. I know that some questions have been raised in the testimony of others, and I am reluctantly restraining myself from hitting them directly.

[The prepared statement of Mr. Haddad follows:]

TESTIMONY

OF

WILLIAM F. HADDAD

CHAIRMAN

GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION

BEFORE UNITED STATES SENATE COMMITTEE

ON

LABOR AND HUMAN RESOURCES

S.2407 "REGARDING THE ANIMAL DRUG AMENDMENTS

AND

PATENT RESTORATION ACT OF 1986"

FRIDAY, JULY 18, 1986

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In 1984, you were presented with a non sequitur. Drugs whose patents had expired still maintained their marketplace monopoly because the FDA did not have a process to approve drugs which entered the marketplace after 1962. There was an active and effective process in place for drugs which entered the market prior to 1962. And to confuse the Congress, the wolf of economic truth was dressed up in hired academic garments of scientific sheep.

You are presented with the same non sequitur with regard to animal drugs. By this legislation, you will remove the governmental barriers to competition in the marketplace and the economic gains will quickly flow to farmers, ranchers, breeders and animal lovers. There is no logic and less science which should permit a patent holder, no matter how many sheep he hires, to extend his marketplace monopoly beyond the life of a patent. And the Congress should not subject a neutral protector of the public health, the Food and Drug Administration, to twist its processes to accommodate a political reality disguised as a technical condition.

The hard facts to support your legislation are available. For veterinary drugs which entered the market prior to 1962, there is a process of sorts in place. There is no process in place to

approve post-1962 drugs. According to FDA estimates, 150 to 175 new chemical or molecular entities have been approved for veterinary use since 1962. Because many of the NCEs are approved for use in more than one species, the total number of post-1962 NDAs approved is around 445. Only a handful of these drugs have been approved for a second manufacturer.

The reason for this paucity of multiple source post-1962 veterinary drugs many sound familiar to this Committee: the costs of unnecessarily re-inventing the wheel, the costs of duplicating tests to demonstrate safety and effectiveness are prohibitive. And as you decided in 1984, they are unnecessary and even unethical.

What are the economic consequences of your legislation? Farmers will pay half price or less for their veterinary products. So will animal lovers. And others. As you know, our experience with human drugs is that when the first competition enters the marketplace, the brand name prices are usually cut in half; when there is more than one competitor, the price usually drops to a fifth of the brand name price. We can expect the same thing for animal drugs when this legislation is enacted.

Let me put some facts behind that statement. A brand name company first obtained approval of the antibiotic gentamicin

sulfate for use in dogs in 1967, and now holds an approval for its use in cats and horses as well. It held that monopoly until less than two months ago when a generic manufacturer took the long expensive road to approval, submitting to the panoply of unnecessary and duplicative safety and effectiveness tests for one species, dogs. The brand is selling (according to one vet wholesaler's summer catalogue) for $31.00; the generic sells for $16.40. I can guarantee that if the Hatch legisliation passes the Congress and becomes law, the price of that drug will drop quickly.

I will submit for the record examples of veterinary drugs for which competition will be quickly available when this legislation becomes law.

In addition to the equity and economic rationales for this legislation there are significant public purposes to be served.

The Federal Food, Drug and Cosmetic Act requires that drugs used in animals be approved by FDA. This is especially important for drugs used in food producing animals. The fact is, that in the absence of competitively priced animal drugs veterinarians are prescribing, and producers are using, generic products approved for use only in humans. Veterinarians, relying on their knowledge and experience, extrapolate the dosage of the human pharmaceutical to the animal species to which the drug is to be administered in order to use less expensive drugs. Two lessons may be drawn from this common practice. First, it illustrates the demand that exists for less costly animal drugs. It also highlights the need for legislation to strip away unnecessary testing requirements that discourage manufacturers from seeking animal drug approvals by which generic products will bear approved labeling and directions for use in animal species.

Enactment of this legislation will also decrease the number of animals slaughtered in order to demonstrate the safety of

drugs for use in animals. FDA's new animal drug approval process requires a demonstration of a drug's safety in the target species (the species in which the drug is to be used) and, in food animals, of the tissue residue to which humans may be exposed. Only by sacrificing animals in the target species can one determine for purposes of submitting an application the safe dose for the animal and residue depletion rates. Such unnecessary testing flies in the face of the Government's intent to decrease, where possible, tests in animals.

Finally, we concur with FDA that approval requirements for veterinary drugs should be substantially the same as those for human drugs. It makes no sense, economically or scientifically, to permit generic versions of pre-62 pioneer drugs to be approved by abbreviated applications, while requiring redundant testing for generic versions of post-62 approved pioneer drugs. Nor does it make sense, administratively, to have different statutory schemes for post-62 new human and post-62 animal drugs. Both have been subject to the same statutory pre-market approval requirements since 1938; only passage of the 1984 legislation created a difference. Enactment of this legislation will restore consistency in regulation.

Thank you for the opportunity to present the views of the Generic Pharmaceutical Industry Association.

The CHAIRMAN. Thank you. As usual, you are very colorful. I have to admit I have really enjoyed working with you, because you really believe very strongly in what you do.

Mr. HADDAD. I miss walking up and down the halls here at 2 o'clock in the morning, trying to get a compromise worked out.

The CHAIRMAN. Well, you have done a great job.

I assume you have reviewed and have had scientific advisers critique the study of Dr. Schwartz and others.

Mr. HADDAD. Yes, I have.

The CHAIRMAN. Could you comment on that?

Mr. HADDAD. Well, first of all, we will comment for the record. On the advice of counsel, I have been advised to restrain my feelings, which are as follows: One, the report is irrelevant; two, it is intellectually dishonest; three, it is insulting to the intelligence of this committee; and four, with all due respect, it was a study designed to reach a conclusion.

You do not have to sit down with an academic and say, "Give me this conclusion." You have to phrase the question properly, as we know from politics and polls—that if you ask the question in the right way, you can get the right answer.

Do you know what it reminds me of, Senator? "Animal Farm," where Napolian, the Stalinist pig, has Squealer, his Goebels, lead the sheep into a repetitive chant every time there is dissent.

In "Animal Farm," the dissent is drowned out by: "Four legs good, two legs bad; four legs good, two legs bad."

In this situation, you have a hired academic covey of sheep, and they try to drown out dissent as they did in the human drug hearings by shouting, "Brand name good, generic bad; brand name good, generic bad."

But as you recall in "Animal Farm," in the end when all the democratic principles become Stalinized and the pig stands on two legs, and the democratic majority who have been fooled and wants to question, Squealer rouses up the academic sheep, and they now sing: "Four legs good, two legs better; four legs good, two legs better."

That is what is happening now in the generic industry. The largest manufacturers of generic drugs are Lilly, Pfizer, Parke-Davis, Lederle, and SKF. They sell—or, they did sell—80 percent of the generic drugs. I use the word "sell" because we manufacture many of those generic drugs for those companies.

I wish we had time, and the procedure was such that we could bring the academics to this stand to answer some questions because I think the study is characterized by one sentence in which they conclude their theoretical summation.

> It is only remotely possible that a generic drug manufacturer, lacking knowledge of exact specifications and manufacturing and formulation processes, could produce a drug precisely chemically and physically equivalent to the pioneer drug.

They have never been to a generic firm. They could not tell you the drugs we make. They do not know our formulations. They do not know our processes. And they do not know at my company when we replace the Danbury label with a branded generic we use the same process, material, and people to make both products.

The generic industry in the United States makes the most sophisticated drugs in the world. And those that are not yet off-patent are made generically in Canada and in Europe. There has never been a question about our ability to do what is necessary. This theoretical stipulation could say, for example, that it is theoretically possible for the salt in the Salt Lake to evaporate, statistically possible, in the next billion years, or by religious miracle. That is what this is all about.

I am quite angry, Senator, because I have been confronted with this kind of study in the past. This one is at least not as complicated as some of the others, but I could take that formula and apply it to, say, the Chicago Cubs and come out with whatever conclusion I wanted. They could win the World Series.

I am sorry for a long answer, against my counsel's advice, but I do not think this study ought to be taken seriously, except in the theoretical sense, and apply it to nuclear energy rather than the experience of 8,000 generic versions of 170 drugs, without a single therapeutic failure. That is experience versus theory. In the absence of experience, you go to theory. But we do not have the absence of experience.

Thanks for your tolerance.

The CHAIRMAN. Thank you. I think what I will do, Mr. Haddad, is keep the record open so you can submit additional comments, and you will give us your analysis of these matters. We would like to have that information prior to our scheduled markup of S. 2407 which will occur, as I recall, on July 30. I would like to mark it up at that time.

Now, you have heard testimony that the patent term extension provision of S. 1093 should be substituted for that which we have in S. 2407 as more reasonable for animal drugs because of the different marketing and testing practices than human drugs.

Would you care to comment on that?

Mr. HADDAD. Well, you know, the rationale, the political compromise that resulted in a human drug which was a tradeoff—the tradeoffs here are identical. I do not think there should be any differences. I think you have established a congressionally accepted compromise, some parts of which I object to, and some parts that the brandname companies object to. But again, you have experience. We have been able to compete, prices have gone down, and patent restoration has been granted. And, aside from that antigeneric warfare going on out there, we have settled into a comfortable economic reality, and the consumers and the Government, as the President and yourself have said, is taking place. I do not see any reason to change what you have considered and compromised in the past.

The CHAIRMAN. Well, I want to thank you.

Mr. HADDAD. Could I say one thing, Senator?

The CHAIRMAN. Yes.

Mr. HADDAD. I am the Sid Wolfe of tissue residue.

The CHAIRMAN. I am not quite sure what that means, but all I can say is it is really foreboding. [Laughter.]

Mr. HADDAD. I know. It raises a red flag here. But I am, and I have been. And I have never seen these famous scientists or the Animal Health Institute come forward and testify about the prob-

lems, either on pesticides or on residue until it became an economic issue.

They are absolutely right. You need to have very careful study of residue. But you do that in the brandname review and in the postmarket surveillance periods, which FDA does very well.

As a practical matter, as a manufacturer, if FDA asked me to stand on my head and whistle "Dixie," I would protest, but I would stand on my head and whistle "Dixie." Any irrational study that they require of us—and sometimes, I think the studies are not required—we will respond. You cannot fight FDA. They are the scientific neutral arbitrator. They are making us do tests now on certain products that I do not think are justified. We make our arguments, we generally lose, and we do the tests.

If they need anymore tissue tests, Frank Young and that group are not going to hesitate to tell us.

The issue here is again a non sequitur, and you hear it in Senator Simon's questions. We are not talking about residue. We are talking about, when you make a generic drug, is it the same process as the brand name; and if it is the same thing, there is no problem, because the statistics and historical evidence is the same.

The truth of the matter is that the differences in generic drugs and brandname drugs are no more than the tolerances allowed batch-to-batch for the brandname products.

So yes, you are right on tissue; yes, you have to look at it carefully, but that is not the issue to separate brand and generic.

Thank you for your tolerance.

The CHAIRMAN. All right. Thank you. We really appreciate your coming.

Our final panel today will include Dr. Steven C. Henry, from the American Veterinary Medical Association, and Dr. Arthur L. Aronson, chairman of the American Veterinary Medical Association Council on Biologic and Therapeutic Agents.

We are very happy to welcome both of you gentlemen to our committee today. We have appreciated everybody summarizing their testimony, and I hope you both will, as well.

STATEMENT OF DR. STEVEN C. HENRY, AMERICAN VETERINARY MEDICAL ASSOCIATION, ACCOMPANIED BY DR. ARTHUR L. ARONSON, CHAIRMAN, AMERICAN VETERINARY MEDICAL ASSOCIATION COUNCIL ON BIOLOGIC AND THERAPEUTIC AGENTS, WASHINGTON, DC

Dr. HENRY. Thank you, Mr. Chairman.

Mr. Chairman and members of the committee, I appreciate this opportunity to express the support of the American Veterinary Medical Association for S. 2407, the Animal Drug Amendments and Patent Term Restoration Act of 1986.

We commend you, Mr. Chairman, in your efforts to resolve some of the inequities in the current animal drug system.

Accompanying me today is Dr. Arthur Aronson, professor of veterinary pharmacology at the School of Veterinary Medicine, North Carolina State University. He will be responding to any questions pertaining to animal drug pharmacokinetics.

And I should parenthetically add that as a general practitioner from Kansas, he will probably have to handle any words longer than "pharmacokinetics" as well.

The health of our Nation's animal population is important to our food supply, it is important to our farm economy and to the emotional health of our people.

As veterinarians, we have several obligations, among them to provide food animal producers with effective and economical services that enhance the health of their livestock, and the productivity of their operations.

We must also assure that the drug use under our direction is proper and safe and will not pose a threat to consumers from harmful residues.

Veterinarians also maintain a strong commitment to companion animal health. The impact of our animal companions on the emotional health of millions of Americans is immeasurable.

Our ability as veterinarians to effectively serve our clients is contingent upon the availability of safe, effective and affordable animal drugs. The AVMA feels that S. 2407, the Animal Drug Amendments and Patent Term Restoration Act of 1986, encourages these goals in two ways: first, by enhancing exclusive marketing privileges for pioneer animal drug manufacturers by restoring patent time lost in the regulatory approval process; and second, by providing an efficient and timely method for approval of equivalent generic drugs when the patent term has expired.

The restoration of patent time lost for a pioneer product manufacturer should be a significant incentive for new product development. We believe this to be particularly important in the animal drug industry where limited markets often deter companies from risking the investment necessary to develop new products.

Additionally, this legislation facilitates the entry of less costly generic products into the market which should result in savings for food producers, pet owners and all consumers.

Veterinarians in the past have not been adequately served with innovative and effective drug products. We currently do not have drugs for animals sufficient to effectively manage the varying and complex disease problems encountered in livestock production. Many antibiotics are becoming less and less effective as bacteria become resistant to their effects.

New antibiotics, to which there would be minimal bacterial resistance, are not being developed and marketed at the rate they are needed. This has led to the increasing in dosages of existing medications above label specifications in an effort to increase antibiotic effectiveness. This extra-label use increases the liability risks for the veterinarian and raises the production costs, as additional safeguards must be taken to prevent drug residue. The development and marketing of more effective and innovative drugs could dramatically change this situation, as well as improve animal health.

Veterinarians favor incentives, such as restoration of lost patent time, that would enhance the animal pharmaceutical manufacturer's ability to recover revenues necessary to continue research and development of new animal drugs. The animal drug market is small in comparison to its human counterpart and functions under

a greater degree of uncertainty as to whether investment costs for new product development will be recovered.

Restoring patent time lost in the regulatory process should reduce some of these risks and uncertainties and provide much-needed financial incentives for the pharmaceutical research.

The American Veterinary Medical Association supports the easing of regulatory requirements for the approval of equivalent generic animal drugs. Veterinarians and animal owners are interested in minimizing the costs of effective medications.

Food animal health, the producer's profit, the veterinarian's service, and the food supply are all compromised when the appropriate treatment costs too much to be practically applicable. Companion animal health is similarly jeopardized when owners feel forced to forego needed medical treatment because of costly medications.

The use of illegally imported, unapproved antibiotics especially in food animals, may be related to the expense of domestic drugs. The Food and Drug Administration has attempted for years to minimize unapproved drug importation, but it does continue. It is our feeling that the need for such black market drugs would be significantly reduced following the introduction of low-cost generic medications manufactured by reputable firms for the animal drug market.

Diminishing the use of imported, unapproved compounds would allay some of the very legitimate concerns over food safety in instances where those products have been used.

The benefits derived through development of less costly generic drugs will be realized by producers, pet owners, consumers and veterinarians alike. In addition, the availability of less expensive quality drugs should reduce the potential for drug residues by reducing the use of unapproved imported drugs and by increasing veterinary involvement in the medication of food-producing animals.

The American Veterinary Medical Association proposes an amendment to S. 2407 to provide statutory authority in the Federal Food, Drug and Cosmetic Act for the class of drugs to be used by or on the order of a licensed veterinarian.

Years ago, the Food and Drug Administration established through regulatory action the category of veterinary prescription drugs. These drugs are, in FDA's opinion, medications for which adequate directions for lay use cannot be written either due to risk to the animal, to the individual handling the medication, or to the food chain.

We commend the wisdom of those at FDA who identified the need, and created the veterinary prescription drug category. Without such action, many of the most effective and potent animal drugs available today could not have been approved for use.

Presently, a problem arises when FDA takes enforcement action against the illegal sale of veterinary prescription drugs. Violators have alleged that FDA does not have the legal authority to create and regulate a category of veterinary prescription drugs for such a category is not recognized in the Federal Food, Drug and Cosmetic Act.

The amendment we propose to S. 2407 will provide that recognition by providing clear and specific authority for a category of

drugs restricted to use by or on the order of a licensed veterinarian.

Court rulings on this issue have been varied, with the latest decision by a Federal court of appeals in Ohio upholding the administrative action of FDA. The FDA's future authority for regulating the distribution of these effective drugs presently remain uncertain.

Clear statutory authority is essential for FDA to continue its present practice of limiting certain drugs to use by or on the order of a licensed veterinarian. Without such statutory authority, some vitally needed animal drugs that require professional handling may be prevented from entering or remaining on the market.

And, rather than read the proposal, I submit that in the paper we have presented for you.

Thank you, Mr. Chairman.

The CHAIRMAN. We are happy to have it submitted.

[Additional material submitted by Dr. Henry follows:]

FURTHER RECOMMENDATIONS AS PRESENTED BY DR. HENRY

Statutory recognition of the veterinary prescription drug category could be accomplished by amending S. 2407 as follows:

VETERINARY PRESCRIPTION DRUGS

Sec. 301

Section 503 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. S353) is amended by adding after subsection (b) the following:

"(c)(1) A drug intended for use by animals other than man which -

(A) because of its toxicity or other potentiality

(B) is limited by an approved application under subsection (b) of section 512 to use under the professional supervision of a licensed veterinarian, shall be dispensed only (i) upon a written prescription or other order of a licensed veterinarian, or (ii) upon an oral prescription or other order of such veterinarian which is reduced promptly to writing and filed by the person filling the prescription or other order, or (iii) by refilling any such written or oral prescription or other order if such refilling is authorized by the other order or by oral order which is reduced promptly to writing and filed by the person filling the order. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale.

(2) Any drug intended for use by animals other than man dispensed by filling or refilling a written or oral prescription or other order of a licensed veterinarian shall be exempt from the requirements of section 502, except paragraphs (a), (i) (2) and (3), if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or other order or of its filling, the name of the licensed veterinarian, the directions for use and cautionary statements, if any, contained in such prescription or other order, the expiration date of the drug, and the identity and quantity of active ingredient or ingredients contained in the drug.

(3) The Secretary may by regulation remove drugs for animals other than man from the requirements of paragraph (1) of this section when such requirements are not necessary for the protection of the public health.

(4) A drug which is subject to paragraph (1) of this section shall be deemed to be misbranded if at any time prior to dispensing its label fails to bear the statement "Caution: Federal law restricts this drug to use or on the order of a licensed veterinarian."

Thank you, Mr. Chairman.

AMERICAN VETERINARY MEDICAL ASSOCIATION
WASHINGTON OFFICE SUITE 828
1522 K STREET N.W. • WASHINGTON, D.C. 20005 • PHONE AREA CODE 202 / 659-2040

July 29, 1986

Mr. Bill Ryan
SD-422
Dirksen Senate Office Building
Washington, D.C. 20510

Dear Mr. Ryan:

I am writing you to clarify my responses to questions posed by Senator Hatch at the July 18 Hearing on the Animal Drug Amendments and Patent Term Restoration Act of 1986. The questions to which I refer regard the statutory recognition of the veterinary prescription drug legend proposed amendment to S. 2407. I was informed that one of my responses may be interpreted as implying that statutory recognition would result in some drugs, presently available over-the-counter, becoming prescription, or vice versa. Let me emphasize, this is not the case. The statutory recognition amendment will not effect the over-the-counter or prescription status of veterinary drugs.

If my responses on the behalf of the American Veterinary Medical Association need further clarification, please do not hesitate to contact me.

Sincerely,

Steven C. Henry, D.V.M.

The CHAIRMAN. You did not have any prepared remarks, Dr. Aronson?

Dr. ARONSON. No.

The CHAIRMAN. You are just prepared to help with the questions; OK.

In the course of your practices, do you frequently encounter situations where, for example, in food animal operations, veterinary prescription drugs actually were bought and sold without a veterinarian being involved?

Dr. HENRY. Yes. I am in a general practice dealing mostly with cattle and swine production. In the animal drug world today in the United States most products for your pet and mine, for small animals, our companion animals and horses, are prescription drugs to be used with veterinary direction.

The CHAIRMAN. Well, are people obtaining these illegally, or how does the process work?

Dr. HENRY. For small animals or companion animals, to some extent, but not much. But now, in the food animal segment, for cattle, swine and poultry, very few drugs are prescription; and because of that, drug marketing is over the counter for the drugs that are not prescription—in other words, they are sold from supply stores, drug wholesale houses, et cetera.

Those few drugs that are prescription are to be sold with the order of a licensed veterinarian. In many cases, they are being sold without such a veterinary order through other houses.

I think it is helpful to understand what kind of drugs we are talking about. In swine, we are talking about the hormones, the ones that we use to induce farrowing in the sow, giving birth; ones to assist during parturition; some that are used in cattle to induce abortion. And these all have similar effects in humans; this is why they are prescription. Yet, because of our marketing, veterinarians—in food animal medicine, veterinarians are involved in less than 20 percent of the drug dispensing or prescription, and it is diverted, yes.

The CHAIRMAN. Well, in your estimation, do you feel that you encounter many situations where prescription drugs illegally obtained were used incorrectly, thereby altering the effectiveness of the drug that would have been, say, more efficacious had it been used correctly?

Dr. HENRY. Yes. In my personal experience, the drugs often are used incorrectly, as adequate directions for their use are not included with them.

The CHAIRMAN. Do you feel the same way, Dr. Aronson?

Dr. ARONSON. Yes.

The CHAIRMAN. Basically, those are the questions I wanted to ask you. We are interested in your amendment, and we will follow through and see what can be done.

I just want to thank everybody for appearing here today. We have had a very interesting hearing. It just brings it more to my attention that we need to do something in this area, and I think everybody will benefit from it if we do it right, so help us to do it right.

[Additional material supplied for the record follows:]

Schering-Plough

PLEASE REPLY TO
Suite 300
1726 M Street, N.W.
Washington, D.C. 20036
Telephone 202-463-7372

Schering-Plough Corporation
One Giralda Farms
Madison, NJ 07940-1000
Telephone 201-822-7000
Telex 219165

July 29, 1986

The Honorable Orrin Hatch, Chairman
Labor and Human Resources Committee
United States Senate
SD-422 Senate Dirksen Office Building
Washington, D.C. 20510

Attn: Mr. William Ryan, Chief Counsel

Dear Chairman Hatch:

We wish to call your attention to erroneous information provided in testimony before the Senate Committee on Labor and Human Resources regarding S. 2407, "Animal Drug Amendments and Patent Restoration Act of 1986," on July 18, 1986.

William Haddad, Chairman of the Generic Pharmaceutical Industry Association, asserted there is a wide price differential between the innovator's animal drugs and the generics. He cited one and only one example in support of his assertion -- our product "Gentocin" (a veterinary antibiotic containing gentamicin sulfate), claiming it was sold for $31.00 whereas the comparable generic sold for $16.40. We must assume that Mr. Haddad was referring to the 50 mg/50 ml vial of gentamicin sulfate, since it is the only strength and size approved for sale by a generic. Our published price for the 50 mg/50 ml vial is $16.40 (for 12 or more vials) --exactly the same price quoted by Mr. Haddad for the generic! Attached please find our January 1, 1986 price list.

The generic industry would have you focus solely on price restraints attributable to generic competition by exaggerating the degree of savings attributable to generics. The committee should be aware that prices on animal drugs are constrained, with or without generics, by competition from other patented products in the same therapeutic class and, particularly in the case of food animals, by the value of the animals to be treated.

We would appreciate your inclusion of our letter and price list in the hearing record.

Yours very truly,

Karl H. Meister
President,
Schering Animal Health

Attachment

SOURCE: "Schering Animal Health Price Catalog," effective 1/1/86, p. 13

Mix-or-Match within this group

GENTOCIN® Injectables

PRODUCT	UNIT OF SALE	NDC-0061	QUANTITY	PRICE	SAVINGS
GENTOCIN® Solution (gentamicin sulfate, veterinary) 50 mg per ml	50 ml multiple-dose vial	-0464-04	1 - 5 vials	$ 20.80/vial	
			6 - 11 vials	18.40/vial	12%
			12 or more vials	16.40/vial	21%
50 mg per ml	100 ml multiple-dose vial	-0464-05	1 - 5 vials	$ 34.00/vial	
			6 - 11 vials	32.80/vial	4%
			12 or more vials	31.20/vial	8%
GENTOCIN® Solution "DOUBLE STRENGTH" (gentamicin sulfate, veterinary) 100 mg per ml	100 ml multiple-dose vial	-0457-03	1 - 5 vials	$ 58.40/vial	
			6 - 11 vials	56.80/vial	3%
			12 or more vials	54.40/vial	7%

HORMONES

PRODUCT	UNIT OF SALE	NDC-0061	QUANTITY	PRICE	SAVINGS
F.S.H.-P.™ (follicle stimulating hormone pituitary for injection) 50 mg A.S. equivalent per vial	carton 1 x 10 ml F.S.H.-P. and 1 x 10 ml diluent	-0195-02	1 - 35 cartons	$ 37.95/carton	
			36 - 71 cartons	35.95/carton	5%
			72 - 143 cartons	34.50/carton	10%
			144 or more cartons	32.95/carton	15%

Mix-or-Match within this group

HORMONES Oral Progestogen

PRODUCT	UNIT OF SALE	NDC-0061	QUANTITY	PRICE	SAVINGS
OVABAN® Tablets (megestrol acetate) 5 mg foil wrapped tablet	box (1 x 240 tablets)	-0867-01	1 - 3 boxes	$ 69.95/box	
			4 or more boxes	62.95/box	10%
20 mg foil wrapped tablet	box (1 x 240 tablets)	-0509-03	1 - 3 boxes	$104.95/box	
			4 or more boxes	94.95/box	10%
5 mg tablet	bottle (1 x 250 tablets)	-0867-03	1 - 3 bottles	$ 63.35/bottle	
			4 or more bottles	56.99/bottle	10%
20 mg tablet	bottle (1 x 250 tablets)	-0509-04	1 - 3 bottles	$ 98.75/bottle	
			4 or more bottles	88.75/bottle	10%

The CHAIRMAN. Thank you so much. With that, we will recess until further notice.

[Whereupon, at 11:28 a.m., the committee was adjourned.]